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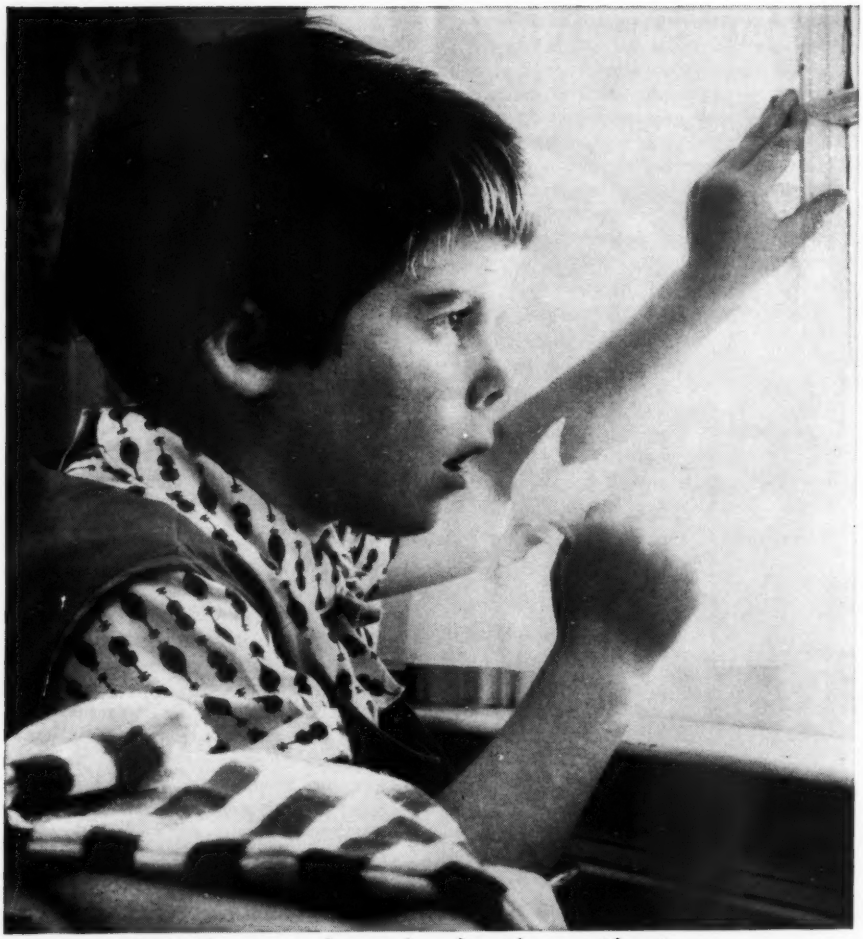

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The Manitoba Medical Review

Vol. 41 OCTOBER, 1961 No. 8

Children's Hospital Grand Rounds

Symposium on the Rubella Syndrome

Chairman: Dr. Howard Reed

Rubella Syndrome Pathogenesis

Dr. Howard Reed

There was a severe rubella epidemic in Australia from 1938 to 1940 and in 1941 Norman Gregg reported 78 cases of congenital cataracts in which there was a history of maternal rubella during pregnancy. In 1943 Swan and his colleagues reported a large series of cases of what we now call the rubella syndrome. The rubella syndrome includes eye lesions such as cataracts, retinal disease and congenital glaucoma as well as hearing defects, cardiac anomalies and mental retardation. Other congenital defects such as cleft palate and hypospadias may also occur.

It has been shown that the embryonic cells most vulnerable to a noxious influence are those in the most active stage of proliferation. When a mother develops rubella there is generalized viremia, and the virus crosses the placental barrier. The virus damages the most actively proliferating cells and may lead to their arrested development or to their death. Thus the nature of the malformations produced depends on the stage of development of the various tissues at the time of infection. A severe maternal infection may cause abortion. Lesser infections cause the varied manifestations of the rubella syndrome, the subject of our symposium.

"Is the rubellar virus the only virus which is capable of producing the so-called rubella syndrome?" We know that it is not. There are reports of cases in which this syndrome followed measles, chicken pox, influenza and other viruses. From this hospital there was a case reported of a "rubella syndrome," if we may call it such, following an attempt by the mother to cause abortion by taking an excessive dose of quinine during the third month.

Reference

Reed, H., Martin, J. K. and Briggs, J. N.: J. Pediat., 46: 182, 1955.

Ocular Lesions

Dr. Edward Burran

The most common eye defect attributed to maternal rubella is congenital cataract, followed by chorioretinitis, microphthalmos, and glaucoma. Cataracts are bilateral in 75% of cases. The critical period in the development of the lens is from the fourth to the eighth week of gestation. Interference during the early part of this period may produce a nuclear cataract, while later infection may give rise to a more diffuse lamellar cataract. In the early studies subtotal central cataracts were most frequently observed, and it was thought that this was a particular type produced by maternal rubella. It has since been observed that rubellar cataracts do not differ from other congenital cataracts and that the type produced is dependent on the time at which the interference with development takes place.

As cataract was the first known defect produced by maternal rubella and since the effect was observed to be peculiar to the first trimester, it was thought that the noxious influence was transmitted by the amniotic fluid. In early pregnancy the lens is exposed to the amniotic fluid while later it is protected by the cornea and lids. However, the finding of other congenital defects of the eye in association with rubella and of defects in other systems removed this evidence for the transmission of the noxious agent by the amniotic fluid.

After cataract, the next most frequent defect due to maternal rubella is chorioretinitis. The usual finding in this type of retinitis is the aggregation of the retinal pigment into clumps, mainly in the posterior fundus around the macular area. While the incidence of cataract is greatest following rubella in the first month, chorioretinitis has a peak incidence following infection during the second month. Rubella chorioretinitis occurs most commonly in the absence of cataract or in the opposite eye in cases of uniocular cataract.

Congenital glaucoma results from interference during the development of the angle. It occurs most frequently following rubella during the fourth and fifth month.

Though many studies of the relation of maternal rubella to congenital malformations have been made, an accurate estimate of the incidence of such malformations is not readily obtained. The earlier retrospective studies gave an incidence of 70% to 100% if the infection occurred during the first trimester. Later studies gave a somewhat lower incidence, but it is probable that all retrospective studies yielded figures which were much too high.

A number of prospective studies have been made, but in spite of the large number of cases which have been followed, the number in which rubella occurred during the early months of pregnancy has always been small.

*Held at the Children's Hospital, Winnipeg, March 23rd, 1961.

Table I
Prospective Studies
D — Stillbirth, neonatal death.
M — Congenital malformations.

Author	Rubella 1st Trimester No. of Cases	D (%)	M (%)	Rubella 2nd Trimester No. of Cases	D (%)	M (%)
Karns	58	10.8	17.2			
Lundstrom	579	5.9	4.5	450	2.1	3.4
Kragman	83	10.8	6.0	...	...	...
Ingalls	63	6.3	15.9	37	7.1	14.3
Greenberg	34	8.5	10.5	77	1.3	2.6
Total		6.9	6.6		2.5	4.0

In Table I, the results of five series are shown. It may be seen that there is a wide spread in the incidence of congenital malformations reported by the various authors. This may stem from a difference in the malformations which were included by the different authors and from the small number of cases represented in some series. Variations in virulence of the virus in different epidemics may also be a factor. Considering Lundstrom's series which comprises the majority of cases in these five series, or taking the total of all five series, one interesting aspect of rubella in pregnancy is seen. This is the observation first made by Ingalls in 1947 that rubella during the first trimester produces a slightly higher incidence of stillbirths and neonatal deaths than of congenitally malformed children.

Table II
Lundstrom, 1951
D — Stillbirth, neonatal death.
M — Congenital malformations.

	No. of Cases	D (%)	M (%)
0 - 4 months			
Rubella	579	5.9	4.5
Exposure — no infection immunity	153	4.4	5.4
— no immunity	344	3.5	1.8
4 months — term			
Rubella	450	2.1	3.4
Exposure — no infection immunity	240	1.6	0.7
— no immunity	508	3.1	1.3
Control	2,226	3.2	1.4

The remainder of Lundstrom's study brings out another facet of the subject. This concerns the effect of maternal immunity to rubella. In Lundstrom's series, the incidence of congenital malformations following the exposure of an immune mother during the first trimester of pregnancy was as great as that in cases where the mother developed a clinical case of rubella. In those cases where a non-immune mother was exposed to rubella but failed to develop clinical disease, the incidence of malformations was not significantly greater than that of the control series.

While attention was drawn to the rubella syndrome by the occurrence of congenital cataracts, eye defects are not the most common sequelae of rubella in pregnancy. Cataracts account for only about 43% of the defects following infection in the first month of pregnancy and decrease to 22% in the second month, and only a small incidence results from later infection.

Table III
Children's Hospital, 1951 - 1960

Congenital Defect	Month of pregnancy during which rubella occurred 1	2	3	4	5
	(number of cases)				
Cataract (all cases)	5	4	5	...	...
Cataract (bilateral)	2	1	2	...	...
Retinitis	1	1	2	...	...
Microphthalmos	1	1	...	...	...
Glaucoma	...	...	...	...	2
C H D	3	4	...	...	...
Deafness	1	1	...	...	1
Retardation	3	2	...	...	1

From 1951 to 1960, fourteen patients have been admitted to Children's Hospital for treatment of congenital anomalies in which a definite diagnosis of rubella occurring in the mother during pregnancy was made, and two cases in which the mother suffered from a fever without a rash. One case of varicella occurring in pregnancy is also included in this series.

The most common defect, as well as the most common eye defect, encountered was cataract; occurring in thirteen of the seventeen patients. Congenital heart disease, mental retardation and deafness followed in that order. Retinopathy was found in four cases, and two cases each of microphthalmos and glaucoma were seen.

With regard to the time of infection (Table III) in all cases of cataract, the infection occurred during the first trimester. This was also true in cases of retinitis and microphthalmos. The two cases of glaucoma followed maternal infection during the fifth month of pregnancy.

In five cases cataracts were bilateral. One case of retinitis occurred without any other eye defect and the other three occurred in the opposite eye in cases of uniocular cataract. As would be expected, the two cases of glaucoma were not accompanied by any other eye defect.

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Congenital Deafness Following Maternal Rubella

Dr. Jack A. Rubin

Gregg and Carruthers both reported series of cases immediately following the Australian epidemic which revealed a very high incidence of deafness in view of all subsequent reports. Gregg noted 111 cases of deafness in 130 cases of maternal rubella (80%), while Carruthers noted 116 cases of deafness following 147 cases of maternal rubella (70%). Other sources indicate deafness to occur less commonly. Lindsay in his study in 1953, reports five cases of maternal rubella where the temporal

bones of the fetus or stillborn were studied. In only one case was there inner ear pathology. Jackson and Fisch report in the Lancet in 1958 on a group of 57 children whose mothers had rubella during the first 18 weeks of pregnancy. Their study appears to be very comprehensive and detailed, and all children were given complete audiometric testing. In their series the figure reported was 30.4%. Lundstrom in reporting on 579 infants surviving maternal rubella noted 4.5% incidence of all congenital defects; Greenberg and Barton noted 12.9% congenital defects in 116 live births; Lamy and Seren noted congenital defects in 23 out of 40 (57.5%) with deafness occurring in only 7.5%. It should be noted that in the latter three studies the incidence is low because of the early age of the infant and because the cases were not followed long enough. As noted by Jackson and Fisch 62.4% of congenital deafness had not been detected by the age of four years, in their series, indicating the importance of detailed hearing tests and follow-up in the diagnosis of rubella deafness.

Time of Maternal Rubella in Relation to Deafness

Murray in a study of 105 Australian children whose deafness was due to maternal rubella observed two peaks of occurrence of the deafness;

(1) at 6 weeks gestation—which corresponds to the beginning of the development of the cochlea.

(2) at 3 months gestation—which corresponds to a rapid development of the organ of Corti.

It was noted that if the maternal rubella occurred in the first eight weeks of pregnancy, 100% of infants born had congenital defects; when rubella occurred in the third month of gestation 50% of the infants had defects. There appears to be no significant correlation between the severity of deafness and the severity of the maternal rubella.

Pathology of Rubellar Deafness

The rubella virus is responsible for increased vascular fragility which results in hemorrhage in the inner ear mechanisms. Malformation and deformity of the auditory mechanism (organ of Corti) occur. The virus reaches the developing sensory structures by the way of the blood vessels and the endolymph and the primary site of damage is the stria vascularis.

Maternal Rubella as a Cause for Congenital Deafness

Goodhill in his study by questionnaire of 904 cases of infantile nerve deafness from all causes, attributed 186 or 20.5% of the cases to maternal rubella. In the same series, 10.3% of the deafness was due to meningitis.

Types of Rubellar Deafness

In all cases the deafness is of a perceptive or nerve type. The deafness is permanent, non-reversible and usually non-progressive. It is important to note that in no case is the deafness complete; there is usually a certain amount of residual hearing which may be utilized in the auditory rehabilitation of the child. Jackson and Fisch in their excellent study noted 14 cases of severe congenital nerve deafness. Of these, six had severe bilateral deafness; three had bilateral deafness with only slight loss in one ear; five cases had a unilateral deafness only. These findings were noted after careful audiometric studies. The audiogram pattern showed a "flat" graph with usually a similar loss of hearing for all frequencies—although a drop for the higher tones was common.

Clinical Aspects

The commonest symptom of severe deafness is delayed or defective speech. One of course realizes that speech develops as the result of imitation of the spoken voice, and the infant who cannot hear, will not be stimulated to produce words. When deafness is not severe or is unilateral there may be very little disturbance of speech. The defects other than deafness are usually detected early in infancy. Thus a cardiac abnormality or congenital cataract will usually be noted earlier than auditory defects which can only be established after thorough audiometric testing.

Report on Cases Seen at the Children's Hospital

Eight cases of "rubella syndrome" were reviewed. These represent all surviving children born of mothers who had rubella in the first trimester of pregnancy. Only those with a definite history of maternal rubella are included.

Table IV
Maternal Rubella and Deafness Incidence

Case No.	Sex	Present Age (years)	Onset Maternal Rubella	Deafness
1.	F.	9	1st trimester	yes
2.	F.	4	1st trimester	?
3.	M.	2.5	1st trimester	?
4.	F.	2.5	6 wks. pregnancy	yes
5.	F.	5	4 wks. pregnancy	?
6.	F.	3	7 wks. pregnancy	yes
7.	F.	20	8 wks. pregnancy	yes
8.	F.	9	4 wks. pregnancy	yes

Incidence

Seven out of eight cases were females. This is probably a coincidence as other series show males and females to be affected in near equal percentages, although there is thought to be a female preponderance. The majority of children were born within the past five years, possibly indicating a more thorough search for maternal rubella in recent years. The onset of the rubella in all cases was in the first trimester of pregnancy. Six of the eight cases had definite evidence of deafness while in the other two, hearing investigation was not carried out for some reason and therefore their hearing status is questionable. Thus in this series 75% of the offspring showed deafness.

Table V
Maternal Rubella and Deafness
Hearing Evaluation

Case No.	Findings	Type of Deafness
1.	60-70 db loss (flat graph)	Bill. Nerve
2.	Not done	?
3.	Not done	?
4.	Responds to "loud noise" only	Bil. Nerve
5	Flat graph	Bil. Nerve
6.	Responds to 100 db only	Bil. Nerve
7.	Loss above 4,000 cps. bilateral, Near normal speech range	Bil. Nerve
8.	50-70 db loss left 65-85 db loss right (flat graph)	Bil. Nerve

Hearing Evaluation

All cases investigated by audiometric studies revealed bilateral nerve deafness. The deafness was severe and the loss involved all frequencies similarly thus producing a "Flat graph." In one case, however, the loss involved only the high frequencies and spared the speech range. This latter patient was the only case which did not require speech or hearing rehabilitation. In two cases, hearing investigation was not carried out.

In conclusion I would like to emphasize that any child whose mother gives a history of rubella in early pregnancy, even if his hearing appears to be normal should be followed until such time as audiometry can be carried out to exclude the possibility of deafness.

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Heart Disease in Infants Following Maternal Rubella

Dr. Gordon Cumming

The prospective studies of McIntosh et al, showed the incidence of significant congenital anomalies to be 7.5% of live births. The etiologic factors responsible for this rather alarming frequency are unknown in the majority of instances. Not more than 10% of all malformations have a clear cut genetic basis (Fraser). Thus the report of a high incidence of defective babies following maternal rubella (Gregg) was received with immediate enthusiasm and hope that the riddle of many of the congenital anomalies might be solved. Unfortunately such has not been the case. The prospective studies of Greenberg and others show that the overall incidence of abnormal babies following maternal rubella probably does not exceed 20% as opposed to the early reports of up to 100%. The expectation that other viral infections during pregnancy might be shown to be teratogenic have not been fulfilled, and in fact it would seem on the evidence to date that other viral infections are not of much importance.

The purpose of this part of today's discussion is to outline the various facets of heart disease occurring in babies born to mothers having rubella during the first part of pregnancy.

a) Types of lesions found:

While atrial and ventricular septal defects, coarctation of the aorta, and Tetralogy of Fallot may follow maternal rubella, patency of the ductus arteriosus accounts for 60% of all cases of congenital heart disease found in these children. In a review by Campbell (b) the incidence of the various lesions in 136 cases of congenital heart disease found to follow maternal rubella was patent ductus 58.1%, ventricular septal defect 17.6%, atrial septal defect 6.6%, pulmonary stenosis 5.9%, Tetralogy of Fallot 7.2% and others 4.6%.

b) Importance as a cause of patent ductus arteriosus:

When the full blown cases of "rubella syndrome" are omitted, a review of 70 cases of patent ductus arteriosus seen at Children's Hospital in the past six years shows that a positive history of rubella during the pregnancy was obtained in only one case. Campbell found that in about 2% of all cases of patent ductus arteriosus there was a history of maternal rubella.

c) Importance as a cause of congenital heart disease in general:

In our work up of a patient with congenital heart disease antenatal factors are always discussed, and whether or not rubella was present is a routine question. Rarely is an affirmative answer obtained. In a review of 100 consecutive cases of ventricular septal defect and Tetralogy of Fallot seen at Children's Hospital in which such information was available, not one case gave a positive history of maternal rubella. Campbell (b) reports a 1 - 2% incidence of a positive history of maternal rubella when all cases of congenital heart disease are considered.

The fact is that maternal rubella is not often the cause of congenital heart disease and the problem, when it arises, chiefly concerns the ductus arteriosus.

As the ductus is a normal structure, and as it remains functionally open for 2 - 3 days after birth, and anatomically open for at least a month, it is reasonable to wonder whether patent ductus arteriosus should be considered a true congenital anomaly. It could, conceivably, arise as a result of some unknown perinatal factors. However, the fact that maternal rubella and rubella only in the first trimester of pregnancy, leads to a high incidence of patent ductus, would seem to offer conclusive proof that this is indeed a true congenital anomaly. This is borne out by some structural changes which separate the normal from the abnormal ductus.

In the last part of this discussion I would like to go over the cardiac findings in nine cases of the rubella syndrome seen in recent years at the Children's Hospital. Case R. H. had no heart disease whatsoever.

Table VI
Cardiac Lesions in the Rubella Syndrome

Case	Cardiac Diagnosis	Comment Re Heart	Other Anomalies
L.B.	PDA	Surgery	Eye, Ear, MR
G.H.	PDA or VSD	Loud murmur in infancy disappeared by age 2	Eye, Ear, MR
D.G.	PDA	Systolic murmur only at one year, then continuous	Eye, Ear, MR
R.H.	Normal		Eye, MR
D.K.	? septal defect	Probably normal, Grade 2 systolic murmur	Eye
J.M.	? septal defect	Loud systolic murmur	Ear, MR
M.R.	PDA, L.S.V.C.	Surgery	Eye, ? MR
B.J.	PDA	Continuous murmur disappeared by age 3	Eye, Ear, MR
J.O.	PDA, pulmonary hypertension	Surgery Systolic murmur only	Eye, Ear MR

Case B. J. had a typical continuous murmur in the first year of life that later disappeared. This in all probability was a patent ductus that closed spontaneously, as there was no evidence of pulmonary hypertension which is another factor that can cause the loss of such a murmur.

Case G. H. had a loud systolic murmur only, and this also subsequently disappeared. This may have been a ductus with a systolic murmur only. However, in most cases the ductus murmur is continuous from early infancy, and the common statement to the contrary is due to a lack of careful listening by trained ears. Another possibility in this case is that there was a ventricular septal defect which closed spontaneously. Long suspected, this event has recently been proven beyond doubt.

Cases L. B. and M. R. had continuous murmurs of the so called typical patent ductus. Case J. O. had only a soft systolic murmur, and was in heart failure at the time of diagnosis. The presence of the other anomalies lead to a more careful antenatal history and the discovery that a rubella like illness had occurred during pregnancy. Heart catheterization established the diagnosis of patent ductus. The pressures in the pulmonary artery were equal to those in the aorta but surgery was successfully carried out. In any infant in heart failure a ductus should be considered and all the more so in this case as a history of rubella was obtained.

Cases D. K. and J. M. had systolic murmurs, and from a chart review it is not clear whether these represent cases of ventricular septal defect, innocent murmur or atypical patent ductus.

Finally case D. J. when first seen had only a systolic murmur. This was proven by analysis of a phonocardiogram, for only a week later a typical continuous murmur was apparent. This serves to illustrate that in some cases the typical continuous or machinery murmur may not be present.

In conclusion, rubella during pregnancy is not an important cause of congenital heart disease. The heart involvement usually consists of patency of the ductus arteriosus, and as surgical cure is usually possible no permanent disability should result. The other lesions that may occur are also amenable to surgical treatment if indicated. Unfortunately many of these cases of congenital heart disease also have the other congenital stigmata associated with maternal rubella. The large British study referred to by Campbell showed that congenital heart disease occurred alone in 50 cases, with cataract in 78 cases, deafness 52 cases, and deafness and cataract in 30 cases. The incidence of mental retardation was not noted. The management of the congenital heart anomaly must take these other factors into consideration.

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Rubella — An Obstetrician's Dilemma

Dr. Otto Schmidt

So grave is the impact of an abnormal child upon a family unit that all efforts must be made to minimize such a mishap, where etiological factors are known. Principal among the teratogenic agents are irradiation, both diagnostic and therapeutic, and virus infections, the foremost offender being rubella.

It seems obvious that all women should acquire rubella before reproduction, that no woman become pregnant within six to eight weeks of the infection, and that each pregnant woman who contacts rubella should be immunized with immune globulin serum. But not so obvious is the correct management of a pregnancy during which rubella is acquired. Whether or not to terminate a pregnancy is the obstetrician's dilemma.

For those whose religious or moral beliefs prevent further consideration of the termination of pregnancy the answer is an enviously simple one. For those who feel there is justification for the termination of pregnancy the answer is found only after the consideration of statistical and psychological factors.

Only a few individuals have had sufficient material for personal observation. Hence, conclusions are based upon statistical evaluation of collected cases. Retrospective studies such as those in Australia concluded that the incidence of fetal anomalies was such that all pregnancies should be

terminated, whereas prospective studies have presented statistics showing a range from 9.7% to 30% of live births. A comparison of such statistics with the incidence of 7.5% congenital malformation in all live births as reported by McIntosh would justify non-interference. However, a comparison of the nature of the anomalies following rubella with the over all picture indicates their seriousness. For this reason many authorities have concluded that there is a place for the termination of a pregnancy complicated by rubella. With this conclusion the author must agree. The decision should not be "when should pregnancy be terminated?", but "when should pregnancy not be terminated?".

The nature of the disease, both its severity and occurrence in epidemic or non-epidemic periods bears no relationship to the severity of the anomalies, while a doubtful diagnosis requires no further consideration. Most important is the time during pregnancy at which rubella occurs. The malformation risk table for children whose mother had rubella during pregnancy devised by Hill and his co-workers demonstrates that one factor dramatically.

Accepting such statistics, and others published, it is apparent that there is justification for terminating a pregnancy where rubella has been acquired in the first twelve weeks of amenorrhea, with little or no justification thereafter.

The rights of the pregnant woman and her family must surely be taken into consideration. Many are the requests for termination of pregnancy, often precipitated by learned and other writings in lay literature. The fear of mental illness warrants consideration. Conversely the patient's age, present family and relative fertility may prove themselves factors to discourage termination of pregnancy.

And of course, last but not least are legal objections, therapeutic abortion being illegal in most areas unless the life of the mother is jeopardized because of the pregnancy, and hospital rulings which forbid such procedure.

The author's series includes four cases of rubella in the first twelve weeks of pregnancy. The first woman requested termination on the grounds of present knowledge (1955) as outlined in the lay press by a physician considered as an authority, and the second was already suffering from a post partum depression, and each was aborted following consultation. The third woman aborted at ten weeks' gestation, while deliberation was underway. And the fourth patient was diagnosed as having rubella by telephone by her pediatrician who had seen her child with rubella. When seen in the office her rash had disappeared, hence the diagnosis could not be confirmed, and the pregnancy was allowed to continue, the outcome being a normal child.

A review of one's minimal experience and that of many authorities allows only one conclusion, namely that it is difficult to justify a dogmatic attitude towards a problem such as rubella complicating pregnancy, each affected woman being a case unto herself.

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Discussion

Dr. H. Medovy:

I am very pleased about this presentation today. I think it was exceedingly well done, and I am particularly happy that our own material was used in the discussion and in the conclusions reached by the speakers. This is an extremely important subject, and I have two or three short points to make. The first is that I think we should remember that Gregg's original study, which was extremely important of course, was a completely retrospective study and that there were opinions expressed at that time that this was an unusual epidemic of German Measles. While there was little doubt that it was German Measles, it was unusually infectious and very severe with many sore throats and many people really violently ill. The Australian physicians agreed that this was not the ordinary type of rubella that they saw. The figures of a risk rate of 80 and 90% which emerged from that study is unrealistic and should be forgotten for practical purposes in the light of the figures obtained from studies of other epidemics. I don't think that we should even think of these figures.

The second point is that deafness is becoming a more and more important problem. We have been thinking of cataracts, congenital heart disease, and mental retardation and, incidentally, deafness; but I think it is now accepted that if people do what Dr. Rubin has done here and continue to observe children born to mothers with rubella in the first trimester (and I think we can forget pretty well about mothers who have rubella after the first trimester) that more and more children are found who have deafness. Some of these cases of deafness are not severe; they are mildly handicapped only and are not too disabled as far as school is concerned. I think that rubella may be the etiological explanation for some cases of deafness that we encounter in school children where there is no history of special disease.

The next point I would like to make is that many people assumed that other virus diseases would also have an effect similar to rubella. That is, if they were sub-lethal virus diseases we would also have trouble with the offspring, and, as Dr. Schmidt pointed out and I think Dr. Reed, this has not proven to be the case. Careful studies were made in Britain in a wonderful seven year study, of the effects on the offspring of rubella and other virus diseases in the pregnant woman and this has just been published. This was a seven year study in Great Britain and Scotland in which were

observed women who had chicken pox, measles, mumps, influenza as well as rubella in the first trimester in order to see what happened to their offspring. Virus diseases other than rubella have not produced a picture like the rubella syndrome at all. Influenza has been associated with fetal death, and this, I think, was known to obstetricians before this study was undertaken and poliomyelitis is associated also with premature birth and with fetal death; but nothing comparable to rubella has developed.

The fourth point I would like to make is the difficulty of making a diagnosis of rubella. We have no diagnostic test for it, and, without being too sensitive about Dr. Schmidt's point about the pediatrician who diagnosed rubella over the telephone, although he did not see the child until three days later, the mother's rash developing on Friday, the only way to be sure about the diagnosis in the mother was to have seen her on the Friday. I think on Monday no one could have made a diagnosis even by 'phone, and it's quite likely that she had rubella; and knowing now that the risk of rubella syndrome in the offspring is not 80 or 90% but something like 15 to 18%, she may have been one of these lucky women who went on and had a perfectly normal offspring in spite of the fact that she had rubella.

The final point I would like to make is about prophylaxis, and I think this is terribly important. Here we have two things that we can discuss. The first concerns "rubella parties" referred to by Dr. Schmidt, and "rubella parties" don't always turn out to be successful even when physicians plan them. There is one "rubella party" on record planned by an enthusiastic physician who cornered all the young females on the block when his young boy developed a rash, and they played together all day for two days, and the only thing that happened is that three weeks later the physician developed chicken pox. Nevertheless, I am in favor of "rubella parties" although we must realize that arthritis can complicate rubella and that encephalitis can complicate rubella in a child and both these may be rather serious complications. They are not common, however, and I think that the risk in the female is so great that for the time being "rubella parties" I think are O.K.

The second point is prophylactic immunization with gamma globulin. Dr. Schmidt referred to this, and I think this is the only measure we can recommend at this time short of the question of abortion which I am not competent to discuss. Gamma globulin has to be given in large doses, 20 ccs. if we are using commercial gamma globulin, and whether it is effective or not depends on where the gamma globulin was first processed. Unless it contains rubella antibody it is useless. If the gamma globulin was processed from blood obtained from soldiers stationed in San Diego where they may not have had German Measles for five years, then conceivably the gamma globulin would be completely useless in prophylaxis. On the other hand, if it is collected in a community in which there has been an outbreak of German Measles and the gamma globulin processed there, then I think it can be reasonably effective; and we have been in correspondence with the Connaught Laboratories hoping that they would obtain blood of this type in areas in which German Measles is epidemic and use this gamma globulin especially for this purpose. But, the final solution will come with prophylactic immunization and this means that, if we can isolate the virus for rubella, we can then produce the modified disease with a suitable vaccine and ensure permanent immunity at least in all females. The possible use of hyperimmune gamma globulin has also been considered.

The speakers this morning have presented the "rubella syndrome" mainly from the point of view of their primary specialties. I think that for paediatricians it is important to remember that the "rubella syndrome" may present primarily as a case of microcephaly and/or mental retardation. Such a case was admitted to the hospital within the last month. The admitting physician was unaware of maternal rubella in the first ten weeks of pregnancy because he didn't take care of the child in the newborn period. The eye and ear complications have not been investigated but the child didn't have cardiac complications. We are hoping that this child will be admitted again later and worked up.

The British study is important because it is a prospective study in which women with known rubella were followed from the time their pregnancy was known and then the results of the pregnancies were assessed. This was a forward looking study in which all women having rubella were studied. Now the answer here fits in with the work of Lundstrom in Scandinavia in giving us what we must consider the true risk involved when a pregnant woman develops rubella in the first trimester. I have taken this table from the British

Table VII
Risk of Defect in Infants Following Maternal Rubella

Stage of Pregnancy at which Rubella commenced	No. of Cases	Infants with Major Defects	
Weeks		No.	%
1st - 4th	12	6	50
5th - 8th	20	5	25
9th - 12th	18	3	17
13th - 16th	18	2	11
17th - 24th	17	1	6
25th and over	19	0	0
Totals	104	17	

Ministry of Health Report on Rubella during pregnancy. The risk is 15.8%, that is 15.8% of the offspring of women who have rubella in the first trimester in the British study showed the major congenital malformations we have discussed. After twelve weeks, 2.2% only showed these major complications, so that instead of the figure of 80 or

90% which has become current we have got to think of 15 to 18%. As far as congenital heart disease, 4.7% of the infants compared with 0.2% of controls; cataracts 4.7% compared with 0.04% controls; deafness 3% compared with 0.08% controls; suspected deafness 3.6% compared with 0.4% controls. We have had a slide made of this so that we can use them here in teaching but these would seem to be the figures that we should think about in future.

Dr. Barsky:

While it is true that there is no other alternative but the use of gamma globulin, the study of Lundstrom throws some doubt on the value of this substance. I think he did one of the best studies thus far. His study showed just as many congenital deformities among those who were immune, if not higher, than those who had never even had German Measles.

Dr. Howard Reed:

I would like to thank our speakers who obviously put quite a lot of time into their preparation. We must also thank Mr. Tony Gibson who produced these tables, some of them at very short notice. I think you will agree they were very clear and well produced.

Obstetrics & Gynecology

Surgery and the Ovary

Maurice Cohen, M.D. (Man.)
Resident-in-chief, Department of Obstetrics and Gynecology, The Long Island Jewish Hospital, New Hyde Park, New York

The surgeon who enters the lower abdominal cavity of the female may encounter conditions which necessitate sacrifice of ovarian tissue. Accordingly, he should be reasonably informed of ovarian pathology, for immediate gynecologic consultation may not always be available. Ovarian disorders may be the cause of lower abdominal pain or may result in a silent abdominal mass. Current concepts of ovarian function emphasize the need for conservation[8].

Systemic Effects of the Ovary

Estrogen is anabolic and favors nitrogen retention. Osteoblastic activity is stimulated and significant osteoporosis has been noted following oophorectomy. Carbohydrate metabolism is influenced, for estrogen acts like insulin and promotes the transport of glucose into the intracellular space. The presence of estrogen, therefore, affords some protection against diabetes mellitus.

Estrogen also reduces the incidence of atherosclerosis[8, 22, 24]. Coronary artery disease is ten to forty times more prevalent in males under forty years of age as compared to a control group of females. It is not uncommon for coronary artery disease to be noted in females following surgical castration[8]. Estrogen has been demonstrated to lower the serum cholesterol, and lack of estrogen is accompanied by alterations in the alpha/beta lipoprotein ratios, alterations associated with increased atherosclerosis. Urinary estrogen estimations are lower in women with myocardial infarct as compared to those free of heart disease of comparable age[15].

The postmenopausal ovary has been shown to maintain a significant estrogen effect in vaginal smears, and over half of the women five to ten years after a normal menopause will show some estrogen effect, considerably more than seen in castrates[16, 20]. This estrogen level is significant, for decade by decade severe coronary artery disease is 10 to 40% higher in castrates as compared to controls[24].

The pituitary-ovarian hormonal balance is disturbed by estrogen withdrawal and an increase in pituitary hormonal activity results[12, 16]. Urinary F.S.H. levels are elevated. Urinary ACTH estimations are also elevated. The pituitary-adrenal hormonal balance is secondarily disturbed and elevated urinary 17-ketosteroid levels reflect the resultant increased adrenal cortical activity. Changes in water balance and a tendency to fluid retention and hypertension are favored by such pituitary-adrenal changes. The increased steroid levels result in depressed thyroid function, and a tendency to myxedema has been noted.

Despite the diminution in blood supply resulting from the ligation of uterine vessels, ovarian function is not altered following hysterectomy, nor is the menopause hastened in these patients[1, 23]. Further, this ovarian function is maintained at a lower level following the spontaneous menopause as is the case normally[20]. This level is significant, however, in affording relative degrees of protection against such conditions as hypertension, atherosclerosis and osteoporosis.

Discussion

Many authorities now favor conservation at any age because of its worth to the total economy[5, 8, 21]. A knowledge of gross ovarian pathology is necessary before judicious ovarian conservation can be practiced. Unfortunately, the frozen section is generally of little value in the diagnosis of ovarian pathology. The opinion of an experienced pathologist viewing the gross pathology is invaluable in arriving at a working diagnosis.

There are reports which indicate that many ovarian specimens which reach the laboratory are either perfectly normal ovaries containing but a corpus luteum or ovaries which show merely functional cysts[4, 11, 17]. Review of such cases often discloses a preoperative diagnosis of acute appendicitis. At surgery, if the appendix is found to be normal, the clinical signs of peritoneal irritation are attributed to the ovary especially if a cystic structure is noted. The increased incidence of specimens from the right side reflects the import placed clinically on pain occurring in the right lower quadrant. Functional cysts must be recognized as but minor variations from the norm. Modest cystic enlargements of this type can be ignored. However, cystic swellings which attain a size of 6 cm. or more have a high incidence of being neoplastic rather than functional and necessitate excision[17]. A working diagnosis can usually be made following the excision and careful examination of the cyst structure and contents.

The presence of adhesions, peritoneal implants, ascites, cysts with solid areas, and papillary excrescences either within the cyst wall or on the surface, all suggest malignant change. Five to twelve per cent of pseudomucinous cystomas and thirty to fifty per cent of serious cystomas show malignant areas at the time of excision[13, 14]. In one series of 349 cases these two tumors made up 46.5% of all primary cancers of the ovary[13].

The solid ovarian neoplasm is more ominous, for it has a high incidence of being malignant and must be differentiated from generally benign solid neoplasms such as the fibroma, thecoma and the Brenner tumor. Twenty per cent of ovarian malignancies are due to secondary spread from primary sites[13]; common sites include the uterus, the gastrointestinal tract and the breast. When bilaterality coupled with a gross diagnosis of ovarian malignancy at laparotomy, a careful examination of the gastrointestinal tract is indicated. Such an examination is imperative in those cases where associated uterine pathology is absent and the gross characteristics suggest the Krukenberg tumor.

Indications for Ovarian Conservation

Hysterectomy for benign uterine disease affords an opportunity for ovarian conservation. Normal ovarian tissue adjacent to benign uterine lesions should be preserved providing the vascular integrity has not been disturbed and examination discloses no pathology. When the indication for surgery is adnexal disease, certain factors must be evaluated before oophorectomy is performed. These factors are age, parity, desire for more children, psychic state of the patient, the psychological worth of ovarian tissue to the patient's personality, and the status of the contralateral ovary. The surgeon who opens the peritoneal cavity for any indication should palpate and/or expose the internal genitalia. Such exploration may reveal silent pathology and result in early diagnosis and treatment.

Functional cysts and true neoplasms occur in children. When operation is performed, ovarian conservation is particularly indicated[6]. The ovary at this time is an abdominal rather than a pelvic organ, and an increased incidence of torsion results. Although ablation of an ovary that is the site of torsion is generally indicated because of irreversible degenerative and necrotic changes, in certain instances exception may be made when the release of torsion restores circulation. Here resection of the benign neoplasm is indicated rather than complete oophorectomy. Because all true neoplasms of the ovary have a significant incidence of bilaterality, the contralateral ovary must be carefully examined. When dealing with the cystic teratoma, one of the commonest neoplasms in children, some authors advocate the bisection of the normal-appearing contralateral malignancy ovary and search for tumor anlage. Even in cases where unilateral malignancy is suspected, simple oophorectomy is indicated. Castration based on an incorrect diagnosis is a far graver error than leaving tissue that necessitates re-operation in this age group.

Complications of Ovarian Conservation

Ovarian conservation involves definite hazards. Subsequent malignancy in retained adnexae occurs, but with the same incidence as in the general population[5, 19]. Likewise, 3% of patients with ovarian carcinoma have had previous pelvic surgery, and this fact has often been misinterpreted[3]. The occurrence of benign ovarian neoplasms also shows the same incidence as in the general population[5, 11, 18]. Although cystic change due to vascular impairment has been described as a sequel to ovarian conservation at the time of hysterectomy, recent series have not substantiated this completely[5, 11]. However, the possibility of such an occurrence necessitates meticulous care in preserving the integrity of the vascular supply to the ovary at the time of operation. Recently, two cases showing inflammatory changes in retained adnexae following abdominal hysterectomy have been reported by us[2]. More recently, we have noted the occurrence of a third case following vaginal hysterectomy. Subsequent surgery was necessary in all of these patients.

Should microscopic examination of a removed uterus, presumably for benign disease, show endometrial carcinoma, re-operation to remove the retained ovarian tissue is indicated. Such repeat surgery must be charged against the policy of ovarian conservation.

Dyspareunia and persistent pelvic pain have been attributed to the retained ovary[9]. This untoward symptom is not likely to occur, if the retained tube and ovary are permitted to remain at their normal site during peritonealization of the pelvis. Here a true evaluation is not possible, for the patient with ovarian conservation following surgery should be compared with the general

population and not with a group of castrates, who undoubtedly exhibit systemic effects of their ovarian extirpation at the expense of freedom from local complications.

Safeguards Prior to Ovarian Conservation

The surgeon accepting the value of ovarian conservation must take safeguards to keep the incidence of morbidity attributable to such retained tissue to an absolute minimum. Firstly, steps must be taken to rule out early uterine carcinoma in these patients who are about to undergo surgery. All patients coming to surgery should have a Papanicolaou smear as a preliminary study. Since adenocarcinoma of the body of the uterus may be as silent as in-situ carcinoma of the cervix, some aspiration technique should be used. Examination under anesthesia, followed by dilatation and curettage, should precede opening the peritoneal cavity in all cases where the indication for surgery is genital in origin. Should the curettings appear grossly suspicious, then the contemplated surgery is best postponed until a microscopic diagnosis on the endometrial tissue is made available. Recently, claims have been made for the efficacy of the frozen section in diagnosing carcinoma[7]. When the surgery performed is a hysterectomy and retention of ovarian tissue is contemplated, it is advisable to open the uterus and examine the endometrial cavity in the operating room.

In those cases with ovarian pathology as the indication for surgery, careful gross examination of the ovary is imperative if adjacent ovarian tissue is to be retained. The excised ovarian tumor should be bisected in the operating room, preferably by the hospital pathologist so that a working diagnosis can be made prior to any further surgery on the contralateral ovary.

Benign ovarian neoplasms have a 5 to 15% incidence of bilaterality[18, 19]. Malignant ovarian neoplasms have up to a 75% incidence of bilaterality[13]. Therefore, adjacent apparently normal ovarian tissue must receive careful scrutiny. The decision to bisect the normal appearing in-situ ovary has to be individualized depending upon the tentative gross diagnosis of the excised tumor, the patient's age, parity, and the surgeon's experience in the handling of ovarian tissue. Such a policy seems highly desirable in the case of the unilateral cystic teratoma.

Contraindications to Conservation

Ovarian conservation is contraindicated in the presence of gastrointestinal or mammary malignancy. The patient, who has undergone conservative pelvic surgery and then years later requires a hysterectomy for benign uterine disease, probably should have an associated complete oophorectomy. The incidence of adnexal complications in this group seems to be higher[10], and a policy of conservation may allow the patient to face the added risks that go with a third laparotomy in the same operative site. The patient with benign uterine disease and menometrorrhagia attributable by exclusion to hypothalamic-pituitary-ovarian dysfunction is said to have a higher incidence of complications in retained adnexae, and probably should have bilateral oophorectomy at the initial procedure[10]. When these latter problems are encountered, individualization is extremely important before ovarian tissue is sacrificed.

Conclusion

Ovarian tissue is beneficial to the total body economy of both the pre- and postmenopausal female. Judicious ovarian conservation is indicated. Such a policy is associated with definite complications and resultant early and late morbidity. Safeguards can be taken to keep such morbidity to a minimum. Careful selection of cases for ovarian conservation is imperative.

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Renal Failure in Pregnancy

Howard D. Karasick, M.D.

Although the syndrome of acute renal failure has been known for many years, it was not until 1947 that Lucke clarified our understanding of the basic pathological physiology.

The problem of renal failure is encountered in all branches of Medicine in a variety of clinical settings. The liberation of blood and muscle pigments after trauma, burns, and transfusion reactions, or in the paroxysmal hemoglobinurias or myoglobinurias, is frequently associated with acute renal failure. Chemical nephrotoxins are especially important in the pediatric age group, with the most frequent offenders being carbon tetrachloride, ethylene glycol, and mercury. The so-called hepatorenal syndrome represents a large group of pathological states with a similar clinical picture. Toxins, infection, shock, and various types of circulatory insufficiency may be included in the etiology of this syndrome.

Any of the above circumstances may be the cause of acute renal failure in the pregnant woman, but pregnancy complications per se account for from twenty to forty percent of all cases of renal failure. Even with modern treatment, including hemodialysis, twenty-five percent of these women die. For these reasons obstetricians are particularly interested in the problem of renal failure.

Renal failure may occur at any stage of pregnancy but it is probably most common in the third trimester and in the immediate post-partum period. The causes during pregnancy may be classified as follows:

1) Circulatory collapse associated with hypotension
   A. Hemorrhage
      1. Ante-partum—abortion
                      ectopic pregnancy
                      placenta praevia
                      abruptio placentae
      2. Post-partum—retained placenta
                      uterine atony
                      lacerations
      3. Afibrinogenemia
   B. Dehydration and electrolyte imbalance—hyperemesis
2) Intra-vascular hemolysis
   A. Incompatible blood
   B. Infusion of distilled water
   C. Abortifacients (quinine)
3) Infections
   A. Septicemia (infected abortion)
   B. Pyelonephritis and necrotizing papillitis
4) Bilateral cortical necrosis
   A. Abruptio placentae syndrome
   B. Dead fetus syndrome
   C. Amniotic fluid embolus
5) Nephrotoxins: mercurials, sulphonamides
6) Eclampsia
7) Obstruction of ureters
   A. Injury
   B. Hematomas
   C. Calculi

The pathology of the renal lesions varies, depending to some extent upon the etiology, which in many cases is mixed. For example, hypertension with superimposed toxemia may be associated with abruptio, traumatic delivery, hemorrhage and incompatible blood transfusion, all in the same patient. Nevertheless certain pathological entities may be distinguished. In eclampsia there is thickening, reticulation and even splitting of the basement membrane of the glomerulus with swollen ischaemic glomeruli. Occasionally in fatal cases there may also be focal necrotizing arteriolitis, usually of the afferent arterioles. In cases with antecedent hypertension there may be hyalinization of afferent arterioles and muscular hypertrophy of interlobular arteries. These changes are focal or segmental and probably involve less than ten percent of the glomeruli. Tubular lesions are not marked. Death in eclampsia is due to renal failure only in extremely rare instances and, if it does occur it is usually due to obstetrical or medical mismanagement.

The basic lesion in bilateral cortical necrosis is extensive endarteritis of the major renal vessels in the non-necrotic portions of the kidney. Eighty percent of these cases occur in association with abruptio placentae. The usual sequence is: extensive abruptio — stillbirth — hypotension — anuria — uremia and death in 7 - 14 days. There is extensive thrombosis of both the interlobular and intralobular arteries and also of the afferent arterioles and glomerular tufts, resulting in generalized cortical ischemic coagulation necrosis of all elements. Secondary effects are present in the medullary tubules. There is always a degree of nephrosclerosis in the arcuate and interlobar arteries proximal to the segments in which thrombosis has occurred. This pre-existing nephrosclerosis, or renal arteriosclerosis, is probably the basis for the vulnerability of some women to cortical necrosis as compared with others. Sixty-five percent of cases of cortical necrosis in pregnancy occur in multiparous patients over the age of thirty, when hypertension begins to appear with more frequency. It is likely that the cases which survive are ones of minor or patchy necrosis with essentially normal renal vessels. This condition can be produced experimentally by staphylococcal toxins, 5 - hydroxytryptamine (serotonin as it occurs in carcinoid tumors), and the vasopressor principle of pituitary extracts. The pathogenesis is intense, prolonged vasospasm of both renal arteries and veins distal to sites of nephrosclerosis, producing vascular paralysis, decreased blood flow, endothelial anoxia, and thrombosis. This results in coagulation necrosis of all structures leading to anuria in 1 - 2 hours.

The renal lesion in excessive vomiting of pregnancy is tubular vacuolization in both proximal and distal convuluted tubules, probably due to potassium loss (hypokalemic vacuolar nephropathy). There is usually mild focal fatty infiltration of the liver associated. Sodium given to hypokalemic patients may result in cardiac arrhythmias (especially in digitalized patients). Even glucose, which causes a decrease in serum potassium, may be dangerous in this situation. Death in these cases is probably due to electrolyte imbalance.

Severe pyelitis may cause death in 3 - 8 days from renal failure due to overwhelming infection. The three commonest organisms responsible are E. coli, Streptococcus, and B. welchii. Pyelonephritis with no treatment or inadequate treatment is a hazard with respect to the immediate risk, chronicity, and especially its relationship to subsequent hypertensive vascular disease.

The commonest cause, however, of acute renal failure in pregnancy is acute tubular necrosis which is often preventable and usually manageable. The mortality rate is 25 percent. It is almost invariably the direct result of shock. If the shock is due to hemorrhage the necrosis is ischemic; if it is due to hemolysis it is hemoglobinuric. The commonest cause of acute tubular necrosis in pregnancy in collected series is incompatible transfusion. Tubular epithelium begins to regenerate within 2 - 3 weeks and if the patient can be tided over this period, recovery of renal function is likely. In these cases, even if toxemia is a prominent feature, it must not be considered the cause of any residual deficits in renal function. Although there may be slight residual renal impairment not associated with nitrogen retention, progressive diminution in renal function does not occur, unless some other disease process causes additional damage. These patients are not more susceptible to subsequent renal injury than are normals and therefore, unless there is more than minimal renal impairment, future pregnancies are not contraindicated merely because of a history of previous acute tubular necrosis.

Although the treatment of established renal failure is the same regardless of the etiology, from a prognostic point of view it is important to differentiate the two main types, bilateral symmetrical cortical necrosis and acute tubular necrosis. The prognosis in the former is poor, while in the latter it is considerably better. Cortical necrosis tends to occur in multiparae over 30 years of age with established hypertension, when it is usually associated with extensive abruptio placentae. In these cases the anuria develops before, or early in, shock. On the other hand, tubular necrosis is not related to parity or age. The cause is shock due to any cause, often hemolysis. There is a period of shock, more or less prolonged, with gradual oliguria, anuria and finally azotemia.

Because the prognosis in renal failure due to abruptio is so poor, definitive treatment in this condition is sometimes hasty and ill-advised. It should be emphasized that in severe abruptio the renal damage probably has its onset in the first few hours, usually before admission to hospital, after which there is little further damage unless there is mismanagement. One must assume that the degree of shock present is due to combined external and internal hemorrhage, and restoration of blood volume is indicated. Termination of pregnancy can be delayed until a propitious moment. There is nothing to be gained from a hasty hysterotomy with the patient already in a precarious condition. This only adds to the shock and contributes to further renal damage. Hypofibrinogenemia must, of course, be watched for in these circumstances.

In pure toxemia, that is, pre-eclampsia, renal lesions occur in less than 50 percent of cases and are restricted to the glomerulus. These lesions are inconstant, infrequent, and inconspicuous. Thickening of the basement membrane of glomeruli is seen in pregnancy without toxemia, and is probably an endocrine effect. There is no significant or characteristic tubular lesion in toxemia. Renal plasma flow in toxemia is reduced if compared with the elevated values that are found in normal pregnancy, but it is within normal limits compared with the non-pregnant state. The reduced urine output that often occurs is related to the diminished glomerular filtration rate. On the basis of the meagre demonstrable renal changes this oliguria must be considered as extra-renal in origin, and is not associated with significant renal damage unless other complications supervene.

Hence the prognosis from a renal point of view in toxemic oliguria or anuria is generally good in that anuria is usually transient unless other factors are added, such as hemorrhage, difficult traumatic delivery, spinal anaesthesia or incompatible blood, all of which may cause hypotension.

Concerning the long-term effect of pre-eclampsia and eclampsia, it may be said that there is no evidence to show that there is any permanent renal damage. The albuminuria and hypertension tend to disappear in pure cases, but persist in cases of toxemia superimposed on pre-existing renal or vascular disease and in cases where there have been additional obstetrical complications causing shock.

With regard to the management of acute renal failure in pregnancy, prophylaxis is a most important aspect. Early and prompt treatment of shock, adequate and carefully matched blood replacement therapy where indicated, avoidance of ill-timed and traumatic obstetrical interference, meticulous prenatal care with attention to the toxemias, hemoglobin levels, malpositions, infections, uterine anomalies and the general health of the patient, are all of importance in preventing, or at least anticipating, conditions which may play a part in the production of renal complications.

When anuria is established the first step in the management should be to determine whether pre-renal or renal failure is present. Post-renal or mechanical obstruction may be excluded by catheterization, including retrograde ureteral catheterization if indicated.

The conservative management of this condition depends on the fact already mentioned, that under favorable conditions tubular epithelium begins to regenerate within two to three weeks. Any attempt to give large amounts of fluid and thereby "force" a diuresis is definitely inadvisable. This practice

was undoubtedly the principal factor responsible for many of the deaths associated with acute renal failure, but actually due to pulmonary edema. Twenty-four hour fluid intake must be restricted to 400-500 ml. plus any measurable fluid loss from the body. If possible, daily weights are the most accurate method of checking the state of hydration. The daily allotment of water should contain as much carbohydrate as can be tolerated. One to two thousand calories per day should be given, orally if possible by the use of syrups, heavily sugared tea or carbonated sodas. If parenteral therapy is necessary as a result of vomiting (a common complication), this can be achieved by the use of concentrated glucose solutions via polyethylene tubing introduced into a large vein. The addition of insulin to these solutions has the transient but beneficial effect of driving potassium into cells as well as ensuring satisfactory glycogen metabolism. Some authors recommend the use of considerable fat in the diet as well as carbohydrate, both of which act as protein sparers, but fat has the disadvantage of increasing organic acids during its metabolism and contributing to acidosis. On the other hand the conversion of glucose to glycogen carries potassium into cells and may thereby inhibit rapid elevation of serum potassium. In the presence of infection caloric requirements increase, and more calories should be provided to prevent protein catabolism. Limitation of bodily activity tends to limit protein breakdown as well. The use of steroid hormones is contraindicated on account of their catabolic effect. Stimulation of protein anabolism by the use of testosterone and norethandrolone (Nilevar) may be of some value.

Electrolyte balance depends on the fact that sodium, chloride, pH and CO_2 combining power are reduced, producing an acidosis which is aggravated by rising potassium, organic acids, phosphates, and nitrogenous wastes. Of particular concern is the elevation of serum potassium to the point of acute intoxication which represents one of the commonest and most serious complications of acute renal failure. Where there has been considerable tissue trauma and interstitial hemorrhage this complication tends to develop earlier. The most serious effect of excess potassium is cardiotoxicity. Cardiac arrhythmias are common, often terminating in asystole. Other symptoms include alteration of the sensorium and muscular weakness. Potassium-free cation exchange resins administered orally or rectally may have some value in this situation.

Calcium and phosphorus levels are also affected. Due to protein catabolism serum phosphate is elevated and this is associated with a drop in calcium levels. If twitching or convulsions develop, administration of calcium salts is only of temporary value. Only by correction of the whole electrolyte picure can this complication be permanently controlled.

With regard to the acidosis, no correction is generally necessary unless it becomes severe enough to cause marked hyperpnea. This does not usually develop unless the CO_2 levels are below 10 mEq./1. In these cases temporary benefit may be obtained by the administration of sodium lactate or bicarbonate.

A progressive anemia is common in the early stages of acute renal failure with the hemoglobin going down to a level of about 8 gm. where it tends to remain stable in spite of progressive uremia. This anemia is tolerated well and, if stabilized, it requires no correction. This is an advantage because the erythropoetic depression and hemolytic element responsible for the anemia do not respond to any known drug therapy. If, however, there is continuous progression of the anemia due to excessive post partum uterine blood loss, replacement therapy with packed or washed red cells (in order to get rid of the excess potassium in the serum) may be resorted to.

Hypertension is a variable phenomenon in acute renal failure. Most patients will exhibit a progressive elevation of the blood pressure secondary to the pathological renal picture, which is usually reversed with the functional recovery of the kidney.

Gastro-intestinal symptoms, including nausea and vomiting, often associated with ileus, are common. These are probably related to the abnormal electrolyte environment and respond to correction by dialysis and general measures.

Antibiotics should be used freely on the slightest indication. Finally, vitamin supplements should be included.

If all these measures fail to control impending potassium intoxication and uremia, the use of some method of hemodialysis becomes mandatory. The employment of this technique has been increasing steadily over the past few years. It was first introduced in 1913, but not used with success until 1943. It has undoubtedly been of considerable value in the treatment of renal failure. The overall mortality rate of this dangerous state due to all causes has been decreased from approximately 90 percent to 53 percent by the use of the artificial kidney.

The indications for dialysis have not been uniformly established. In general, clinical signs and symptoms of uremia are regarded as more clear-cut indications than abnormal biochemical findings. There is said to be a reliable correlation between daily increments in blood urea nitrogen and the necessity for dialysis. Conservative therapy alone, without dialysis, will usually suffice if the daily rise is 10 mg. percent or less. A daily rise of 10-30 mg. percent usually requires one or more dialyses, while if the figure exceeds 30 mg. percent the procedure has to be repeated many times. Other investigators recommend the use of dialysis before the development of uremic symptoms. By employing it daily as a prophylactic measure in anuric patients with

indwelling arterial and venous catheters, these workers have prevented the onset of uremic symptoms for as long as three weeks. These patients remained ambulatory and continued to eat unrestricted meals.

Evidence of potassium intoxication is probably the most unequivocal and urgent indication for dialysis. This is obtained from rising serum estimations, the onset of cardiac arrhythmias or minimal electrocardiographic deviations. It is advisable to resort to dialysis before persistent emesis brings about increased electrolyte derangement or before coma develops with its hazard of superimposed pulmonary infection.

Another candidate for hemodialysis is the patient who remains virtually anuric for 6 to 7 days. It is at this time that severe clinical deterioration is imminent and dialysis should be initiated before this late stage is reached. If one procrastinates and allows the patient to lapse into the terminal stages of acute uremia, characterized by coma, convulsions or cardio-pulmonary complications, the ideal time for dialysis has passed. Irreversible and permanent damage to the circulatory and nervous systems has been wrought and dialysis at this time may improve the patient only temporarily.

If pulmonary edema develops, sometimes caused by the over-administration of fluid, hemodialysis may be used immediately, not only to correct the apparent chemical derangements but also to reduce the edema by a process of ultrafiltration.

Following most dialyses there is impressive clinical and chemical improvement. A 6 to 8 hour dialysis may reduce the blood urea nitrogen by 50 to 75 percent with a similar reduction in creatinine and uric acid. Smaller solutes such as Na, K, Ca, and Cl are rapidly restored to normal. Serum bicarbonate levels are elevated by 5 - 10 mEq/1. which in large part represents the removal of organic and inorganic acids. With clinical improvement of the sensorium, elimination of nausea and emesis and a general return of well-being are to be expected. The patient can afterwards tolerate another 3 - 7 days of anuria. If no diuresis is evident at the end of this time, dialysis should be repeated.

Because of the recent mechanical advances in dialyzing machines, including increased efficiency and simplicity and decreased bulk and cost, most other methods of dialysis, including gastro-dialysis and intestinal perfusion, have been neglected. However, the use of short-term, intermittent peritoneal dialysis has the advantage of simplicity, while with present methods infection is no longer a hazard. Although not as effective as the various forms of artificial kidney, it can be repeated daily and it affords an effective means of controlling both fluid and electrolyte balance as well as nitrogen retention.

Certain other methods and techniques have been tried over the years with varying degrees of success. Most of these involve attempts at autonomic denervation of the kidneys and include the following:

1. Unilateral decapsulation. This may occasionally be followed by immediate diuresis and eventual recovery.

2. Infiltration anesthesia of the renal pedicle. Excellent results have been reported from this method in a series of cases reported from France.

3. Paravertebral block.

4. Spinal and continuous caudal anesthesia.

5. Intravenous procaine.

6. Intravenous infusion of concentrated serum albumin.

When urine output attains a level of 500 ml. in 24 hours, the diuretic stage has been reached. One may now see a dramatic increase in urine volume, amounting to a doubling or trebling in each 24-hour period until a maximum of 3 to 4 litres per day is reached. The early part of this diuretic phase represents a partial restoration of renal blood flow and a return of glomerular function with continued depression of tubular function. Hence the urine formed is equivalent to a glomerular filtrate without benefit of tubular reabsorption. Consequently there is a loss of water and electrolytes, especially of sodium and potassium. The diffusion of urea through the functionally impaired tubules causes the blood urea nitrogen level to continue to rise during this early diuretic phase. The patient's condition may threfore continue to be precarious from the additional loss of important electrolytes.

In a matter of several days, however, tubular function shows signs of being restored with the leveling off or decline of the high urinary output and the gradual decrease in the blood urea nitrogen. The serum electrolyte pattern begins to approach normal and the patient shows marked clinical improvement. This phase, termed the late diuretic phase, represents the return of all aspects of kidney function. Complete recovery may take several months and long-term follow-up studies have shown that renal function tends to remain just below the lower limits of normal. This degree of renal function, however, is compatible with a normal life expectancy.

Medicine

Modern Concept of the Etiology and Pathogenesis of Acute Glomerulonephritis

S. K. Cheuk, M.D.

In discussing disease of the kidney with albuminuria, Richard Bright[1] once remarked, " . . . it may be fairly asserted that no other disease is more interesting in its history and origin, affords so many instances of the consent and dependence of the different functions upon each other, gives so much scope for pathological observations, or so fertile in facts interesting to the cultivation of animal chemistry, as the disease of which we now speak." Despite the passage of the years, increase in knowledge in understanding of Bright's disease, these remarks are singularly apt today.

Many clinicians and pathologists have a rather clear concept of the etiology and pathogenesis of acute glomerulonephritis. However, careful analysis of published reports on nephritis, both in man and experimental animals reveals many gaps in our knowledge as well as many facts which are difficult to reconcile with the present theory of the causation of nephritis.

It is generally agreed that acute glomerulonephritis in man is not the result of direct bacterial invasion. It is etiologically related to antecedent infection of the respiratory tract and the skin caused chiefly by B-hemolytic streptococcus. Because nephritis follows rather than accompanies this infection, it sems likely that the renal reaction is not directly due to bacterial toxin or bacterial metabolites. This inflammatory reaction represents a hypersensitivity to bacterial protein, or an autoimmune response to renal components altered by reaction with bacterial products.

Natural History

Clinically the initial attack of acute glomerulonephritis begins with appearance of dark brown or smoky urine, often accompanied by swollen ankles or hands and swelling of face and the eye. These signs characteristically appear one to three weeks before respiratory infection. Demonstration of proteinuria, hematuria and red blood cell casts and frequently hypertension established the diagnosis.

Usually this disease is not severe and clinical improvement is noted within a few days or weeks. However, in 5% to 10% of the patients, chronic glomerulonephritis develops. In such patients, persistent albuminuria may be the only manifestation of continued renal disease. Later signs of decreased renal function appear. The factors responsible for the initiation of the attack seem to be infection with group A hemolytic streptococcus. The relation seems to be well established. Since infection with group A streptococcus involves the respiratory tract and less commonly the skin, the patients with nephritis usually have a history of sore throat, scarlet fever or skin infection. The signs of nephritis usually develop after recovery from the acute phase of the bacterial infection.

Etiology — Bacteriologic and Serologic Studies

The fact that scarlet fever may proceed nephritis,[2] that group A streptococcus may be isolated from many patients after symptoms of nephritis develop, and the antistreptolysin titre of a serum obtained during first few weeks of illness is usually high, attest that glomerulonephritis is a complication of streptococcal infection. Strain of group A organism might vary in their ability to produce renal disease as shown by Seegal and his co-workers.[4]

The first method used to determine whether strains of streptococcus vary in their nephritogenic capacities was the serological classification of organisms isolated from oropharynx of patients with acute glomerulonephritis. With this technique, most strains obtained were type 2. The association of this type with nephritis has been recorded throughout U.S., Canada, Australia, England, Chili and Japan. In one epidemic in Minnesota, a new serological type "Red Lake" has been identified. Types 4 and 25 have been isolated in sporadic cases in U.S. This is not a satisfactory method, since by the time signs of nephritis develop, few organisms may be present in the nasopharynx and in some cases, these isolated organisms may represent an old infection or a recent cross infection.

A second and more accurate method for establishing the relative role of various serologic types in the production of nephritis is the study of streptococcal infection throughout the period in which the renal complications develop. In this way, the original infecting strain can be identified before onset of nephritis, and regular cultures and clinical and laboratory observations will assure that a cross section in a new serological type did not occur.

A third method is the determination of type specific antibodies in serum or whole blood obtained from patients who have recovered from an attack of acute nephritis. Type-specific antibodies which persist for several years develop in individuals infected with group A streptococcus. Studies in Cleveland area[5] show that most patients who recovered from an acute attack of hemorrhagic nephritis show antibody against type 12 streptococcus, whereas serum from patients with nephrosis showed no antibodies. Recently, Braude[6] demonstrated antibodies against Red Lake strain in individuals with nephritis in Minnesota. Since antibodies to specific serological types may persist for several years, an increase in type specific antibody against a nephritogenic organism is the best

indication of its etiological significance. The presence of this antibody indicates immunity against specific type. It has been frequently said[7], that patients recovering completely from acute glomerulonephritis rarely, if ever, develop a second attack. Recurrence may be explained on the basis that patients may be infected with more than one nephritogenic type and freedom from recurrence may be due to type specific immunity. It is more difficult to explain recurrence in patients with chronic nephritis. Preliminary studies indicate that serum from patients with chronic nephritis contain no type specific antibodies against nephritogenic streptococcus. This suggests that the pathogenetic mechanism in exacerbations of chronic nephritis differ from those involved in the initial attack of glomerulonephritis.

Perhaps one of the puzzling features of acute glomerulonephritis is that many patients exhibiting classical signs of the disease fail to show B-hemolytic streptococcus in culture. This really causes a lot of confusion regarding the etiology of glomerulonephritis. Bacteriologic studies[8] suggest that the number of streptococci decrease rather rapidly following an acute streptococcal infection, so that a single oropharyngeal culture cannot be considered sufficient to exclude the possibility of infection with these organisms. In addition, certain biological characteristics of nephritogenic streptococcus may be responsible for these variable bacteriologic results. It has been reported that pneumococci could cause glomerulonephritis[9], but hypertension and edema are not a characteristic feature.

Pathology

Many of our concepts of nephritis have come from extensive contributions of pathologists. The lesion in kidney is considered to be limited to the glomerulus. There is proliferation of the endothelium, infiltration of the glomeruli with polymorphnuclear leucocytes, escape of erythrocytes into the capsular space and thickening of the basement membrane. There may be obliteration of the capsular space and development of crescents. According to Bell[10], the changes in glomerulus may be seen during the course of several infectious diseases, and therefore may not be specific. However, correlation of the pathological findings with the clinical disease and with bacterial and serological data should make possible a precise differentiation between these conditions.

Experimental Nephritis

I. Heterologous Protein Nephritis

Glomerulonephritis and cardiovascular lesion have been reported in rabbits in which serum sickness was induced by administration of horse serum, purified serum albumin or serum r-globulin. A single large dose or several small doses of these antigens resulted after a latent period of 8 to 10 days in the appearance of fever, proteinuria, hematuria and cylindruria. Histological studies of kidney tissue show glomerular enlargement with swelling and proliferation of the endothelial and epithelial cells of the tufts as well as thickening of the glomerular basement membrane. Tubular lesions were uncommon. In addition to renal lesion, myocarditis, endocarditis, and generalized arteritis accompanied by lymph node hyperplasia occur with variable frequency.[11]

Concurrent immunologic and histologic studies in heterologous protein hypersensitiveness have shown that the lesion of glomerulonephritis after a single injection of antigen appear during the last stages of antigen elimination and are maximal just before the appearance of free circulating antibody[12]. After free antibody appears, the renal lesion as well as cardiac lesion regress[12]. These findings indicate that renal and cardiac lesion occur at a time when antigen-antibody may both be present and are consistent with the hypothesis that the lesions result from antibody-antigen combination.

Additional evidence that nephritic lesions are the result of antibody-antigen reaction is given by the demonstration that complement decreases in animals given foreign protein during the period when antigen is rapidly disappearing from circulation and renal lesions are appearing. In 1938, Ogawa and Sato[13] suggested a relationship between complement and development of experimental nephritis when they found low serum level of complement coincide with the onset of nephrotoxic nephritis. This fall in complement may be due to antibody-antigen reaction involving the kidney and may therefore play an important part in the pathogenesis of nephritis, but proof of this hypothesis is still lacking.

II. Nephrotoxic Renal Disease

Masugi was the first to demonstrate that chronic renal damage resulting from injection of nephrotoxic or anti kidney serum. His result was confirmed by Smadel[14]. This serum is prepared by injection, as antigen, of homogenized kidney tissue from one animal into another animal species. To produce nephrotoxic renal disease, the anti kidney serum is then injected into animal species from which the kidney tissue was originally obtained. Nephritis has been produced by this technic in rats, rabbits, and dogs with nephrotoxic serum made in ducks, chickens and rabbits. Lesions in these animals are essentially similar.

It is reported[15] that glomerular tissue, especially glomerular basement membrane, contains the nephrotoxic antigen. Glomeruli absorb nephrotoxic activity from anti kidney serum. Radioautography and fluorescence microscopy using antikidney serum with radioactive or fluorescein labels demonstrate the localization of labelled antibody in glomeruli, particularly in glomerular basement membrane. This may indicate the participating antigen and the site of reaction of nephrotic serum[16]. Placental tissue is also said to produce nephrotoxic serum. This is probably due to

presence of basement membrane material, antigenically related to basement membrane of glomerulus.

III. Streptococcal Induced Nephritis

Because of the epidemiologic evidence of the apparent role of certain types of group A streptococcus in the etiology of glomerulonephritis, a number of attempts have been made on experimental animals by injection of streptoccocus or streptococcal products. In some incidents, signs of inflammation of kidneys have been noted; but not quite characteristic of human glomerulonephritis. Recently Duval and Hibbard[17] immunized rabbits with streptococcus obtained from patients with scarlet fever. Later when these animals were challenged with intravenous or intraperitoneal administration of streptococcal lysate, renal lesions were produced. "Epithelial crescents" formation, hyaline thrombi of glomerular capillaries, hemorrhage into the capsular space and necrosis of capillary tufts were found. They believed that lesion in kidney was mainly due to damage by streptococcal endotoxin rather than to allergic reaction because they isolated a bacteriolysate from streptococcus broth culture that produced toxemia and death when given by single injection to animals. Kay[18] has suggested that a soluble product of the streptococcus enters the circulation and lodges in the kidney. In the host, antibody to the streptococcus or to a combination of the streptococcal product develops, and the resulting antibody-antigen union produces renal damage. Seegal[19] has suggested that the original union of the streptococcal product may produce a sub-clinical kidney damage that would make the kidney more susceptible to the subsequent AB-AG union.

Several of the studies that have been discussed have in common one feature: they suggest in varying degrees the presence in the circulation of a substance or substances directed against some components of the renal tissue, i.e., basement membrane. In the nephrotoxic nephritis the nephrotoxic antibody localizes in the glomerular basement membrane, producing an initial inflammatory reaction. This is succeeded by an autogenous antibody response in a pattern corresponding to the deposition of the nephrotoxin. When foreign protein has been injected intravenously in the rabbit, producing glomerulonephritis, the autogenous antibody response has again been localized in glomerular basement membrane. These studies strongly suggest two possibilities that foreign protein in both instances either localized in basement mmbrane long enough to combine with the antibodies produced in response to it, and thereby produce tissue damage, or that the foreign protein in some way affects the membrane so that the new altered structure became auto-antigenic.

There are several possibilities for the mechanism of tissue damage by antibody-antigen reactions according to experimental and clinical investigations. Raffel[20] mentioned that antibodies themselves may have a direct toxic effect on cells, as seems to be true of autohemolysin cornered in causation of paraxysmal hemoglobinuria. An Arthus reaction may occur in which the vascular damage produced by the immune reaction results in tissue ischemia and necrosis.

Wiener suggested[21] another mechanism for the production of tissue damage as a result of immune mechanism — that necrotic lesions might be produced by blockage of capillaries with agglutinated sensitized red blood cells. Germuth[22] suggested soluble antigen-antibody complexes which occur with antigen excess are themselves responsible for production of allergic lesions. He has demonstrated that in experimental serum sickness[23] the most severe lesion develops during the phase of rapid immune antigen elimination. It is during this phase that antigen is present in excess of antibody. It is apparent that much has already been learned, but that further work is required to gain a deeper insight into the mechanism(s) by which tissue damage occurs in immune reaction.

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Some Aspects of Anticoagulant Therapy

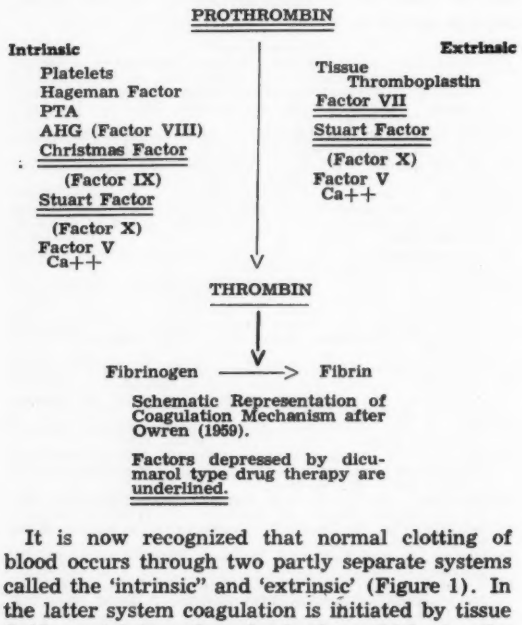
John Foerster, M.D.

Introduction

The coumarin anticoagulants are now being employed on a wide scale in the treatment of thrombo-embolic disease. Although originally used mainly on a short term basis they have in recent years been relied upon extensively for long term continuous treatment in the hope of preventing further thrombo-embolic episodes. The object of this paper is to review recent investigations dealing with the effects of such medication on the clotting mechanism and to study methods proposed for the effective control of treatment.

Before considering these points a brief review of the modern concept of blood coagulation would seem indicated.

Figure 1



Schematic Representation of Coagulation Mechanism after Owren (1959).

Factors depressed by dicumarol type drug therapy are underlined.

It is now recognized that normal clotting of blood occurs through two partly separate systems called the 'intrinsic" and 'extrinsic' (Figure 1). In the latter system coagulation is initiated by tissue fluid containing thromboplastin, which in the presence of factors V, VII, X and Ca++ leads to the conversion of prothrombin to thrombin. On the other hand the clotting factors necessary for the intrinsic system are all found in the circulating blood. Coagulation is initiated by contact with a foreign surface, probably involving the intermediary action of Hageman factor and PTA(40). The thromboplastin formed in whole blood is an extremely powerful one, but a time consuming reaction is required for its generation, extending over several minutes and depending in part on the type of foreign surface involved. In contradistinction to the extrinsic system, the conversion of prothrombin to thrombin by blood thromboplastin is not dependent on the accelerating action of factor VII, though V, X and Ca++ are still involved in the reaction.

With either system the final stage in blood clotting involves the conversion of fibrinogen to fibrin by thrombin. This is the only stage in the coagulation process which can be observed directly and all other reactions are inferred from their effect on the occurrence and speed of formation of the actual clot.

The Action of Anticoagulant Drugs in Relation to Specific Clotting Factors

When the hemorrhagic disease caused by spoiled sweet clover was first studied, early investigators thought the defect to be simply due to a marked drop in prothrombin levels[34]. These studies seemed to be substantiated several years later by Quick[32] who reported the first quantitative investigations of the effect of sweet clover on prothrombin, after having developed a method for determining what he considered to be prothrombin levels. Subsequent work has shown that this test, later to be known as the "Quick one stage prothrombin time," is by no means prothrombin-specific. Modern investigators have repeatedly demonstrated that prothrombin, although affected by prolonged dicumarol therapy, is reduced to a lesser extent and less rapidly than other factors[17, 8, 11]. Donald et al[6] suggest that the alteration in plasma prothrombin levels is variable and insignificant and is unlikely to influence the one stage prothrombin time. In support of this contention the investigators quote a case of uncomplicated prothrombin deficiency described by Biggs[2] whose patient exhibited an almost normal Quick prothrombin time despite an actual prothrombin level of only 11%.

Douglas[8], using two stage methods, found the mean prothrombin content of a large series of random specimens from patients being treated with tromexan to be 65%. The same author also suggests that the level of prothrombin found depends on the duration of action of the drug used, the longer acting compounds leading to a more profound depression of prothrombin. The findings of Donald et al[6] are in agreement with this view. These workers report a series of four coumarin treated cases in whom the continuation of bleeding was associated with very low levels of prothrombin as measured by two stage methods, but with no gross deficiency of factor VII, resulting in an almost completely normal Quick one stage determination. However, Johnson et al[14], using indanedione, a compound with a shorter duration of action than dicumarol, found prothrombin levels to be depressed to 20% of normal within three days of treatment.

It is now well known that the anticoagulant action of dicumarol type drugs is not restricted to a depression of prothrombin levels but that a whole family of factors, known as the "prothrombin

complex" is involved. This complex includes prothrombin, factor VII, Christmas factor (factor IX) and the Stuart-Prower factor (factor X). The synthesis of all these principles occurs in the liver and is dependent on the availability of an adequate supply of vitamin K.

Factor VII was the second component of this complex to be discovered and linked with the action of dicumarol drugs. Quick[33] recognized that "prothrombin" was composed of two active principles, A and B, the former gradually disappearing from plasma on storage (prothrombin proper), the latter being stable (factor VII). It was this stable factor which he found to be depressed in dicumarol poisoning and vitamin K deficiency. Later other workers corroborated Quick's findings[7]. Unfortunately many of the early studies are inconclusive as they fail, even in retrospect, to differentiate between the effects of dicumarol therapy on factor VII and on factor X. Recent work indicates that factor VII levels drop rapidly after the institution of anticoagulant therapy, reaching low levels within 24 hours, whereas factor X remains elevated for several days before starting to decrease gradually [5, 37], reaching levels of 7 - 20% of normal in approximately a week. In cases of bleeding due to prolonged marcumar treatment, extremely low levels of factor X are found, though the Quick time remains within the therapeutic range[1]. Bachman et al[1] suggests that bleeding in cases of prolonged marcumar treatment is principally due to depression of factors IX and X. Bleeding and the lowering of these factors to critical levels do not occur for 6 - 8 days.

In 1955 Douglas showed that serum from patients under therapy with coumarin drugs leads to defective thromboplastin generation when substituted for normal serum in the thromboplastin generation test[8]. In the same year Sise et al[36] described a group of five patients maintained on phenindione for 27 days whose sera failed to correct the defect in prothrombin consumption of two cases of proven Christmas disease. Two patients out of three tested also failed to correct the defect in thromboplastin generation. Bachman et al[1] showed that depression of Christmas factor in patients treated with marcumar did not occur before 6 - 8 days. However, McElfresh and Ozge[25] found Christmas factor to be depressed after treatment with tromexan or dicumarol for only 24 - 48 hours. These findings are in agreement with those of Douglas and Mair[1] who report that the effect of phenindione therapy on this factor develops quickly, reaching low levels 48 - 72 hours after initiation of treatment. According to most studies the fall in the factor VII complex precedes slightly the fall in the affected thromboplastin factors, Christmas and Stuart factors[11]. On giving vitamin K to dicumarolized patients factor VII always rises first, prothrombin a little later, whereas Christmas factor does not rise for 10 - 14 days[14].

Site of Action of Dicumarol Drugs

Perfusion experiments have demonstrated that isolated livers from dicumarolized rats do not destroy prothrombin, but that the normal isolated liver is capable of increasing the prothrombin activity of blood deficient in it due to dicumarol treatment[22]. Jaques et al[12], working with C^{14}—labelled dicumarol, found a rough quantitative relationship between the prolongation of the Quick one stage prothrombin time and the amount of C^{14} labelled dicumarol concentrated in the liver. As much as 20% of the injected dose was found in this organ in unchanged form.

Some investigators have extended the observations on the site of formation of the prothrombin complex and, therefore, the site of action of dicumarol. Jurgens[15] showed that prothrombin may be formed in experimental animals despite extensive liver damage, if large doses of vitamin K are administered. He implicated the reticulo-endothelial system as the most likely extrahepatic site for the formation of the involved factors. Later Jurgens[16] showed that prothrombin, proconvertin (factor VII) and proaccelerin (factor V) may be formed and sometimes return to normal levels following total hepatectomy in experimental animals when large doses of vitamin K_1 are administered.

Slätis[38] injected rats with Thorotrast which, like some other colloid agents, is selectively ingested by the RES and blocks certain of its functions. In the liver the dye was exclusively concentrated in the Kupffer cells. No hepatic parenchymal damage could ever be demonstrated. Within a period of 6 - 12 hours both prothrombin and proconvertin were shown to be markedly depressed to levels ranging from 6 - 18% of normal. The recovery to normal levels was rapid, being completed in 24 - 48 hours. Thorotrast also markedly blocked the ability of vitamin K to restore prothrombin and proconvertin levels in dicumarolized rats.

In order to prove extrahepatic synthesis of prothrombin and proconvertin the same author subsequently investigated the effect of vitamin K administration on hepatectomized rats[38]. Immediately after hepatectomy eleven animals were given vitamin K intravenously. Ten animals served as controls and received no vitamin K. It was found that in control animals prothrombin and proconvertin levels dropped to 40% of normal within 1 - 2 hours. In comparison to their starting levels these factors remained relatively unaffected in animals given massive doses of vitamin K. These findings suggest an extrahepatic synthesis of both prothrombin and proconvertin.

Mechanism of Action

Dicumarol has no inhibitory action on blood coagulation in vitro. Whereas heparin interferes with the reaction of coagulation, dicumarol interferes with the manufacture of a number of the reactants. This action of the drug is highly specific.

The view of early workers that dicumarol produces its effects on the basis of non-specific hepatotoxic properties could never be substantiated. Meitus and Wasserman[26] concluded that their studies on the hepato-toxic effects of long term bishydroxycoumarin therapy did not produce any conclusive evidence of appreciable hepatic parenchymal damage in patients who had previously not suffered from liver disease.

The structural resemblance of coumarin drugs and vitamin K as well as the interrelation of their actions has led some investigators to postulate that both vitamin K and bishydroxycoumarin have an affinity for the apoenzyme necessary for the synthesis of the prothrombin complex[4]. Whereas vitamin K forms the prosthetic group for this apoenzyme, coumarin seems to act as an antivitamin.

Martius[23] suggested that synthetic anticoagulants inhibit oxidative phosphorylation in liver mitchondria. This inhibition could also be demonstrated in cases of vitamin K deficient animals, whereas addition of vitamin K caused an increase in oxidative phosphorylation. It was suggested that vitamin K may function as a carrier in terminal electron transport and thus possibly link electron transport to oxidative phosphorylation. Lowenthal[19] was indeed able to demonstrate inhibition of DPNH oxidase activity of heart muscle preparations by dicumarol. However, on testing various coumarin analogues, some of which possess anticoagulant activity while others do not, he found no correlation between anticoagulant properties and inactivation of DPNH oxidase. Jaques[13] suggested that the effect of dicumarol on oxidation mechanisms may account for the toxic effects of the drug on the heart and blood vessels but not its specific effect on prothrombin.

The replacement of a methyl group by a chlorine atom in a biologically active compound may result in an analogue with inhibitory activity. Since vitamin K_1 contains a methyl group, its chloroanalogue has been synthetized by Lowenthal and tested for its ability to inhibit the antidotal activity of vitamin K_1 against coumarin anticoagulant drugs [20]. When the chloro-analogue was administered intravenously to warfarin treated animals, 1.24 mg. and 0.62 mg./kg. of body weight completely blocked, whereas 0.31 mg./kg. of body weight significantly reduced the antidotal effect of 1 mg./kg. of vitamin K_1. The same results are obtained if the dosages of vitamin K_1 and its analogue are increased by identical multiples of the original dose, suggesting a competitive type of antagonism between the two agents[21]. The same relationship has not been demonstrated for all antagonists of vitamin K.

The problem of the mode of action of dicumarol is far from being solved. At present it seems most likely that the clotting factors involved are synthesized by an enzyme system of which vitamin K is a coenzyme. As pointed out by Lowenthal[20], all compounds with vitamin K activity are paraquinones and thus may function as components of an electron transport system. Coumarin anticoagulant drugs must interfere with this system by depleting it of its coenzyme, as their effect is readily reversed by vitamin K.

Control of Therapy

The purpose of laboratory control is to ensure that the dosage of drugs for a particular patient is neither inadequate nor excessive. In most medical centres the policy is to administer the maximum dose of the drug which is compatible with safety. Laboratory methods are intended as an aid in determining these limits of safety. Such tests should ideally reflect the total defect induced in the patient's clotting system and be simple and reliable even in the hands of technicians who are not trained in coagulation techniques[28].

The most commonly used test is the one stage prothrombin time of Quick[31]. It has been generally accepted that if the one stage prothrombin time is less than three times as long as that of normal plasma, hemorrhage is unlikely. If the prothrombin time is more than three times normal, hemorrhage may occur[3]. However, these criteria are crude and generally unsatisfactory. Some patients may be overdosed for prolonged periods of time without evidence of bleeding[29], whereas others may bleed with prothrombin times in the "safe therapeutic range" [6, 18]. The method of expressing this safe therapeutic range as a percentage of normal prothrombin activity (15 - 30%) with reference to dilution curves seems to be equally unsatisfactory.

The rather poor correlation between Quick's one stage prothrombin time and bleeding is probably due to the multiplicity of lesions produced by dicumarol drugs. As can be gleaned from Figure 1, these agents affect both the intrinsic and the extrinsic systems. However, Quick's method reflects the extrinsic system only, and is thus principally sensitive to changes in factor VII and Stuart factor. In addition dicumarol therapy is said to decrease capillary fragility[30, 43, 45] and the adhesiveness of platelets[10, 44], neither of which influence the one stage time but may predispose to bleeding. The test is also largely insensitive to changes in prothrombin, very low levels of which, even in the absence of obvious factor VII depression, may nevertheless lead to hemorrhagic episodes[6].

The type of thromboplastin used also influences the test enormously. Russel viper venom, for instance, is insensitive to variations in factor VII concentration and should therefore be avoided[3, 29]. The source of thromboplastin and even batches of brain extract from the same source may lead to considerable differences in interpretation. Previous administration of heparin also interferes with the one stage prothrombin time[42]. This makes it imperative to wait 4 - 6 hours following use of heparin before proceeding with the test.

In spite of all these obvious disadvantages the one stage test has as yet not been replaced by other methods for routine use. Hicks and Bonnin[11] concluded that factor VII and Stuart factor activity are in most cases reasonably well related to the activity of the affected thromboplastic factors, though this relationship is not absolutely constant. Lampert and Roller[18], however, found good correlation between the thromboplastin generation test and the Quick test in only 25% of cases. In 11 of 41 patients there was in addition a marked increase in thromboplastin generation above 100% before treatment was instituted. This was not reflected in any of the other tests (Quick, P+P, Thrombotest — see below). Hicks and Bonnin[11] stress the importance of keeping the results of the one stage test below 25% to prevent a rise of thromboplastic factors to normal levels.

Recently Thompson[41] described a modification of Quick's one stage test for the control of outpatients on anticoagulant therapy. The test is done on fresh capillary blood immediately after it has been taken, thus shortcircuiting the intrinsic system before blood thromboplastin has had an opportunity to generate. In a controlled series of 200 tests run in parallel with Quick's one stage test the incidence of variation of more than two seconds is only 1.2%.

Other Tests For Control of Therapy

The one stage method gives little change in clotting time before the factor VII concentration is reduced to 20 or 25% of normal. Simple dilution methods have the disadvantage that factor V and fibrinogen are also diluted and physiological variations in these factors may have an unpredictable effect, causing a considerable increase in random and irrelevant variation[3].

In Owren's P+P method, so called because it was thought to give a combined estimation of prothrombin and proconvertin levels, this variation has been eliminated by the constant addition of prothrombin free plasma rich in fibrinogen and factor V to a dilution of plasma to be tested[27]. Thus this system contains in excess all factors of the extrinsic system which are not affected by anticoagulant therapy. Brain thromboplastin and calcium chloride are added to the mixture and clotting times recorded. The combined prothrombin and proconvertin concentration is read in terms of clotting time from a standard dilution curve prepared by testing dilutions of normal plasma. It seems that the P+P method is to be preferred to the Quick one stage method. Whereas the incidence of hemorrhage in Owren's series is 1.3 episodes per 100 patient-treatment-years, the comparable figure for the American series of Wright, controlled by Quick's method, is 125[3].

Mayer and Connell[24] proposed the use of whole blood clotting times for control of anticoagulant therapy, aiming at a prolongation of clotting times to 15 - 20 minutes from a normal of 9 - 10 minutes. Unfortunately these methods measure only the changes occasioned in the intrinsic system. The complete lack of hemorrhagic complications reported by these authors is probably due to the fact that patients were grossly undertreated by conventional standards (upper limit of 30% of prothrombin activity) during 69% of treatment days in one group and 36% in another.

Some workers suggest that heparin clotting time methods may give a better indication of the overall stage of coagulability[39]. However, this method also reflects changes in the intrinsic system only. In addition the test is influenced by factors not changed by anticoagulant treatment such as platelets[28] and is generally unsuitable for routine control of large numbers of patients.

Recently Owren[28] has described a method for measuring in a single operation the coagulation activity of all factors affected by anticoagulant therapy. Normally the formation of thromboplastin by the intrinsic system takes several minutes, depending on the type of activating surface. The extrinsic system is initiated by tissue fluid already containing thromboplastin, resulting in the formation of a clot in 12 - 15 seconds, thus making it impossible to detect the activity of the slower intrinsic system. In Owren's "Thrombotest" the two systems have been adjusted to operate at approximately the same speed. The intrinsic system has been accelerated by the introduction of an active cephalin preparation while the extrinsic system has been retarded by the use of a thromboplastin of low activity. The reagent has been completely freed of all principles influenced by anticoagulant therapy but contains all other factors in excess. The method has been adapted for use on whole blood, either capillary or venous, or citrated plasma. The therapeutic range for anticoagulant therapy as controlled by this method is considered to be 10 - 30% of normal. The test is shown to be sensitive to all four factors — prothrombin, factor VII, factor IX and factor X.

Lempert and Poller[18] have evaluated Thrombotest extensively. They conclude that the therapeutic ranges of the Quick test and Thrombotest are not directly comparable, the accepted lower limit of the Quick test (15%) either being too low or the lower limit of Thrombotest (10%) being too high. In three cases of hemorrhage described, Thrombotest data showed levels below the therapeutic range and the thromboplastin generation test showed thromboplastin generation to be below 5%. In contrast the Quick test showed prothrombin activity to be in the therapeutic range, i.e., above 15%. This points to the possibility of the lower limit of the Quick stage method being too low. Good correlation between Thrombotest and the thromboplastin generation test was shown in 50% of cases. This figure seems to be acceptable in view of the fact that the test purports to measure changes in both the extrinsic and intrinsic systems. Owren's P+P method and Thrombotest always showed good correlation.

Seaman[35] found the capillary blood Thrombotest to be a useful and convenient test-system for regulating anticoagulant drug dosage. In contradistinction to Lempert and Poller, Seaman found a fair degree of correlation between Thrombotest, the P+P activity assay and the Quick one stage prothrombin time.

Summary

1. The anticoagulant action of dicumarol type drugs is principally due to their effects on a family of coagulation factors known as the "prothrombin complex." This complex has been shown to include prothrombin, factor VII, Christmas factor (factor IX) and Stuart-Prower factor (factor X).

2. Dicumarol and its analogues probably exert their action by interfering with an enzyme system necessary for the synthesis of this complex. Vitamin K is suggested to act as coenzyme in this system. It is proposed that the reticulo-endothelial system is the site of synthesis for the prothrombin complex.

3. Methods for the control of therapy are analyzed and their relative faults and merits discussed. It is suggested that both Owren's P+P test and Thrombotest give better results than Quick's one stage prothrombin time.

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. . . If you are determined to become a charlatan, the first thing to do is to take full advantage of the present taste for obscurity in expression and of contemporary leniency towards unsupported assertions. You will by that means avoid exposing your incapacity for thought and the meagreness of your knowledge. Thus would otherwise be serious drawbacks may actually become advantages. And on no account neglect to pepper your writings with jibes at the inadequacy of reason and assertions about the trustworthiness of instinct. With regard to your personal behaviour, which is so important in the career of a charlatan, I have very few suggestions to offer, but be careful not only to praise a competitor whom you have obviously surpassed, and then, most emphatically, for the least of his talents. This will give others a high opinion of your generosity and at the same time do him very little good. And if you praise yourself, which you must do from time to time, adopt a plaintive and indignant tone as if you had been forced to do it by the injustice of the world. Boast frequently in talking to women, but in talking to men content yourself as a rule with speaking in carelessly disparaging tones of great men and great work. Also when you attack your enemies, attack them en bloc; this has an air of courage while it is far less dangerous than attacking individuals. In choosing subjects select, if possible, those on which better men than you have, after much research and thought, failed to reach a conclusion. Such subjects will supply you with hopeful readers, and spare you the toil of original enquiry. Where evidence for your assertions is wholly lacking, a generous but discrete use of the words "of course" is to be recommended.

"Affable Hawk" (now Sir DESMOND MacCARTHY), in the New Statesman.

Theraputics

Evaluation of a New Anorectic Combination in the Treatment of Obesity

L. F. Kocsis, M.D., L.M.C.C., M.C.G.P.
Mall Medical Group, Winnipeg, Manitoba

The privilege of eating all one wants, once reserved to the very few, is so commonplace in North America today that millions of people now are significantly overweight. Many obviously obese individuals blame their adiposity on "glands," but the truth is, that for every case where there is an organic cause, there are hundreds that are attributable simply to bad eating habits. These people could be termed the victims of "functional obesity," and they need our help.

Partly because of the hypnotic effects of mass media, many of us smoke, drink and eat more than we should and, at the same time, try to counteract these excesses, especially the latter. For the person who is grossly overweight, such social patterns can undermine all attempts to stabilize his diet. He hates being fat, but is often unable or unwilling to go through the necessarily prolonged period of concentrated effort needed to improve his condition. We all know about the various diet fads which crop up regularly; obese patients may try many of them before failure to establish a satisfactory pattern of weight-loss will bring them to the physician.

As with many other complex disorders, there is no single solution for the treatment of functional obesity. The most common cause of overeating is psychic disturbance; it frequently compensates for feelings of tension and frustration. In taking the patient's history, the psyche is the most important area to probe, apart from questions about family incidence of obesity, hypertension, diabetes or gall bladder disease. On asking the reason for wanting to reduce, I have found that the most common motive is vanity, followed by fear of ridicule.

As always, we physicians must remember that we are dealing with individual humans and not just case numbers. The standard, rigid reducing diets frequently fail, in the absence of a proper doctor-patient relationship, because we tend to forget that every patient is different. Each of us has conditioned habits of eating, taste, appetite, expenditure of energy and metabolism. For each of us, the gratification received from food-consumption varies in type and intensity.

Bowser et al[1] and others[2, 3, 4] have pointed out that diet therapy alone for obesity almost invariably fails. Having tried different diets myself with varying success, I have come to the conclusion that Plotz's "social diet"[5] is one of the easiest to follow and most appealing to patients. According to this regimen, regular portions of food are simply reduced by ¼ or ½, and no whole milk, cream, ice cream, gravies or saturated fats are allowed. Weight loss on such a diet comes gradually, but steadily, and is not as shocking to the physique as some of the crash programmes that patients occasionally resort to.

Naturally, the concomitant use of a drug which reduces the appetite can help a person who is dieting. But there are additional problems which the overweight patient must face: the visual temptation of foods he sees other people eating, the strain of remembering what he himself must not eat, and the necessity of taking his medication faithfully.

To combat the psychic factors which may cause overeating or lead to a failure of treatment, the administration of a tranquilizer can lessen the patient's emotional discomfort and bolster his will to reduce. A combination of dextro-amphetamine, a well-known anorectic agent, and prochlorperazine, one of the phenothiazines, has recently become available. Since its makers claim that this combination can produce marked suppression of appetite and simultaneously relieve the patient's anxiety and tension, I decided to try it in my practice for a period of six months.

In order to evaluate the success of the trial medication in treating functional obesity, I selected cases according to the following factors which often cause this condition:

psychic disturbance
social and cultural pressure
family eating habits.

In addition, only patients who seemed to be strongly motivated to lose their excess fat were chosen. I agree with Allison that, "The prognosis for weight reduction is good if the motive for reducing is strong, poor if either the motive or the character of the food-addict is weak."[6]

Method

I prescribed one capsule of the test combination to be taken before breakfast, usually about 7-8 a.m. (there were a few cases where the optimal result appeared with the dose taken at 10 o'clock). Each capsule* contained 15 mg. of dextro-amphetamine sulfate and 7.5 mg. of prochlorperazine.

I tried to see patients weekly during the first month, and once a month thereafter, since I believe that strict medical supervision and reports by phone are just as important as drugs and diet. Repeated contact with the physician reinforces the desire to lose weight and also makes the patient less sensitive about his condition.

*Supplied as "Eskatrol Spansule" capsules, by Smith Kline & French, Montreal.

Fourteen male and 36 female patients were included in this 6-month study. Most were more than 25 lbs. overweight. The amounts by which initial weights exceeded desirable weights† are as follows:

Pounds Overweight	No. of Patients
5-10 lbs.	2
10-20 lbs.	6
20-30 lbs.	15
30-40 lbs.	9
40-50 lbs.	8
50-60 lbs.	4
60-70 lbs.	2
70-80 lbs.	2
80-90 lbs.	1
90-100 lbs.	1
	50

Ten of the 50 patients had essential hypertension, seven had tension headache. Two women had migraine, and one had peptic ulcer.

Results

Individual maximum weight loss achieved during the study was as follows:

Weight Loss	Males	Females
1-5 lbs.	1	3
5-10 lbs.	4	8
10-15 lbs.	3	6
15-20 lbs.		9
20-25 lbs.	2	2
25-30 lbs.		1
Failures:	4*	7*

Although most of these patients had not been able to lose much weight on previous diets and medications, there was a mean weight-loss of from 10 to 15 pounds during the test period. I thought this encouraging because, for one thing, it proved to them that they could reduce without starving themselves; the prospect of having to do without food when they crave it is horrifying to overweight patients.

As expected, the number of patients who lost 20 lbs. or more was small. Stunkard and McLaren-Hume[7] carried out an extensive search in the medical literature of the last 30 years and found, with remarkable uniformity, that less than 30% of patients treated had succeeded in losing more than 20 pounds. In their own series of cases, the figure was only 12%. This is similar to my results—of 42 patients who were 20 lbs. or more overweight to begin with, 5 managed to lose that much by the end of the study.

Important, too, was the patients' emotional reaction to the trial program. A good many overweight people undergo a change of personality when beginning a new reducing plan. They know that ahead of them lies a period of self-discipline and some physical discomfort; this tends to make them irritable and depressed, particularly if past experience has been unfruitful. This was not the case with the test medication; in addition to feeling pleased with their improved appearance and physical condition, patients said that being on a diet did not upset them as much as before, even though weight-loss was quite gradual.

In the future, there will occasionally be relapses, even in those who respond best to treatment — especially since eating has assumed reward status for the majority. Nevertheless, this combination appears to suppress appetite and at the same time keep emotions on an even keel. Therefore, I feel that it gives both the patient and the physician a good chance to reach the ultimate goal, a reasonable body-weight and the sound eating habits which will help to maintain it.

The low incidence of side effects was a reassuring feature of the test combination. Only 3 patients complained of any symptoms which could have resulted from taking it: 1 patient became unsteady and developed vertigo, 1 experienced insomnia and tinnitus, and 1 noticed increase in appetite. Parenthetically, it was most unexpected and gratifying to find that 8 of the 10 hypertensive patients became normotensive while on the medication, and have remained so. Although one would not expect a central nervous system stimulant such as dextro-amphetamine to produce a lowering of blood pressure, I find that at least one previous report[8] mentions this phenomenon.

Summary and Conclusion

A combination of dextro-amphetamine and prochlorperazine was tried in a series of 50 overweight office patients. Dosage was one capsule daily, taken in the morning. At the end of the six-month trial period, 39 (78%) had experienced a satisfactory loss of weight — in most cases amounting to more than 10 pounds.

The psychic effects of the test medication were also generally good. Patients adhered to the prescribed diet, faithfully took their capsules, and seemed to undergo relatively little emotional difficulty in doing so. Judging by my results, it would appear that this combination of dextro-amphetamine and prochlorperazine can be a valuable adjunct to diet and close supervision in the treatment of overweight.

†Based on a table issued by the Canadian Department of Health and Welfare, Ottawa.

*Of these 11 patients, 4 did not return for final evaluation, and 6 of those who failed to achieve a satisfactory weight reduction had originally been from 60 to 100 lbs. overweight.

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Pediatrics

A Review of Tuberculous Meningitis in the Pediatric Age Group at St. Boniface General Hospital

J. Greene, M.D.

It is the purpose of this presentation to consider tuberculous meningitis in the pediatric age group from the standpoint of its significance, pathogenesis, clinical picture and complications.

Tuberculous meningitis is defined as a tuberculous infection of the meninges of the brain or spinal cord, or, of both. It is usually believed that infection reaches the brain by the blood stream. Experimental work however suggests that the meninges are very resistant to blood infection, even when large numbers of tubercle bacilli are injected into the carotid artery. On the other hand the meninges are readily infected when the injection is made directly into the subarachnoid space.

Rich and others have shown that in many cases, it is possible to demonstrate a tuberculous lesion in the brain, choroid plexus and even the meninges. These lesions are regarded as the source of the meningeal infection. When one of these lesions is sufficiently superficial to discharge bacilli into the subarachnoid space or ventricles, tuberculous meningitis results.

The source of the cerebral lesion is from blood dissemination to the cortex or choroid plexi, or directly to the subarachnoid spaces. The lesion is usually secondary to pulmonary tuberculosis.

Pathologically speaking, there is formation of a creamy or greenish somewhat gelatinous exudate at the base of the brain extending from the chiasma to the cerebellum. It usually fills up the spaces and glues together the surfaces of the brain. In some cases, one can see some tubercles along the lines of the vessels of the Circle of Willis. The convolutions of the brain are flattened and the sulci narrowed — owing to the hydrocephalus which is nearly always present and which is caused by exudate over the roof of the 4th ventricle.

Microscopically, definite tubercles are usually conspicuous by their absence and the same is true of giant cells. Diffusely arranged epithelioid cells and areas of caseation necrosis are the characteristic feature. The subarachnoid space is filled with lymphocytes, plasma cells and polymorphonuclear cells but here again, patches of necrosis indicate the nature of the process.

The charts of pediatric patients with tuberculous meningitis admitted to St. Boniface General Hospital during the period of 55-60 were reviewed.

These cases were evaluated on the basis of individual status, contact with tuberculosis, clinical signs and symptoms, course and complications.

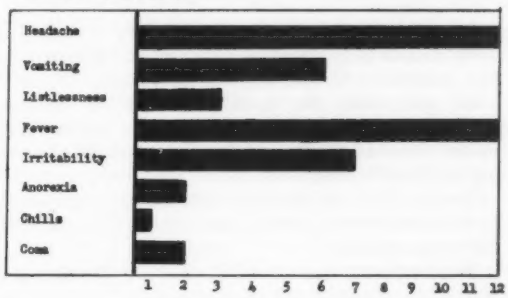
Results

Age	Sex	Race
Mean — 3.6 years	There was no sex difference	5/12 Indian
Range — 1 - 6	6 male and 6 female	1/12 Eskimo
		2/12 Polish
		1/12 English
		1/12 Hebrew

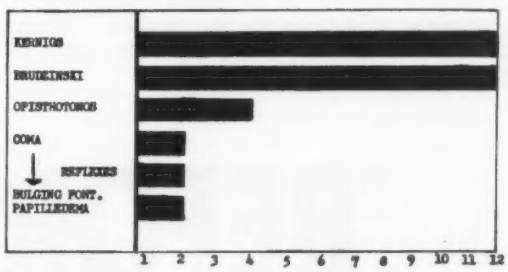
Duration of Symptoms Before Admission

Range — 1 - 28 days
Mean — 7.2 days

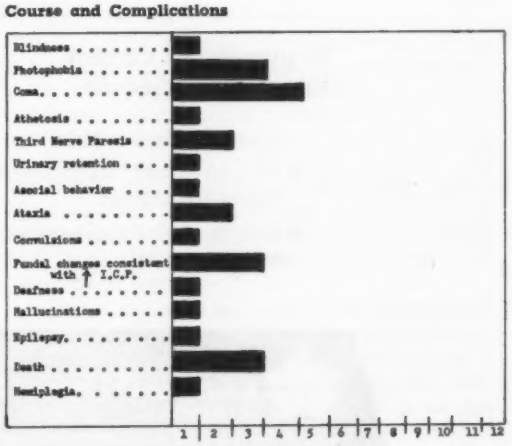
Entrance Complaints



Physical Signs at Admission



Course and Complications



Laboratory Results

	Mean	Range
Hb.	12.3 grams	8.8 — 15.3 grams
ESR	41 mm.	9 - 70 mm.
WBCs	12,900	7,900 - 22,000
Neutrophils	57	37 - 77
Lymphs	30	8 - 49
Bands	4	1 - 9
Monos	2	1 - 6
Urinalysis	3 pus/HPF	0 - 9

Mantoux Positive

5 of the 12 patients had a positive Mantoux skin test.

Lumbar Puncture

	Mean	Range	Normal
Protein	434	66-2650	15-45 mgm. %
Sugar	27	0-47	50-70 mgm. %
Cl.	378	332-433	425-455 mgm.%
WBC	131	5-284	0-5 mgm. %

X-Ray

5/12 showed chest x-ray evidence of tuberculosis.
3/12 showed cranial pressure on x-ray of skull. Evidence of increased intracranial pressure on x-rays of skull.

In this series the common entrance complaints were headaches, vomiting and fever. Coma also was a striking entrance complaint.

On admission, the usual evidence of cerebral irritation were found but opisthotonos was present in one third of the cases. This is not usual according to Russell Brain.

During the hospital stay, 25% of the cases were noted to have photophobia and 12% developed third nerve paralysis.

None of these cases showed evidence of choroidal tubercles. Illingsworth et al stated that 50% of the cases developed these lesions. However, in all cases ophthalmologists did not review the patients and this "fact" may not be accurate.

None of these Cases Showed Evidence of Miliary Dissemination of Tuberculosis. Lincoln stated that 27% of the cases have miliary tuberculosis. This result tends to favor the theory that there is first a superficial lesion in the brain which discharges miliary tuberculosis into the subarachnoid space.

25% of the cases treated at this hospital died of the complications of the disease. Before the introduction of streptomycin, death occurred in almost 100% of the cases. The usually stated prognosis varies between 10 and 50% mortality, even with present day treatment.

40% of these cases showed x-ray evidence of pulmonary tuberculosis. The usually quoted figure is 25% showing either enlarged hilar nodes or active primary complex (Brain).

The Mantoux test was positive in only 47% of these cases showing that it is notoriously unreliable as an aid to diagnosis. This point has been brought out by previous authors.

In Summary

1. The pathogenesis, significance, clinical picture and complications of tuberculous meningitis have been reviewed.

2. This series tends to support the theory that tuberculous meningitis has a basic etiological factor; a primary lesion in the brain which discharges into the subarachnoid space, causing meningitis.

3. The Mantoux Test is unreliable as an aid to diagnosis in the face of active tuberculosis.

Special thanks to Miss C. Stankiewich and the Medical Records Department of St. Boniface Hospital for their aid in obtaining required records.

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Editorial

S. Valsrub, M.D., M.R.C.P. (Lond.), F.R.C.P. (C.), F.A.C.P., Editor

Why Not Medicine?

In the past not too long out of mind, when the dry dust of depression lay heavily upon the land and career opportunities were as scarce as the dental appurtenances of the proverbial hen, the number of medical students on this continent was thought to be in excess of the demand for doctors and of available facilities for training. As a consequence various methods of "selection" were devised —a favorite one being the "interview," wherein a momentous confrontation would be effected between the student and his appraisers in an atmosphere, needless to say, none too conducive to relaxation. An inescapable question directed at the freshman, one intended to clarify motivation, yet hardly contributory to the easing of tension was: "Why do you want to be a doctor?"

Why indeed? The bizarre replies to this unanswerable question with reasons ranging from professions of unbounded sympathy with suffering humanity to intentions of discovering a cure for bubonic plague carried little conviction To some sensitive souls they were to become a source of embarrassing memories to blush at during moments of unhappy recall.

The situation has changed. No longer is there a surplus of aspirants to a medical career. Expanding opportunities in various vocational fields are enticing young people away from Medicine with a resulting drop in the number of applicants to Medical Schools. This development which threatens to blight the normal growth of Medicine and endanger the health of the people, is causing great worry, particularly to those who are intimately concerned with medical education, as attested by the spate of articles, editorials and symposia dedicated to this pressing problem.

It may be worth recalling at this point the old "interview," and its "key" question. Can they be put to good use by the simple command of "about turn"? Since the goal today is the very opposite of what it was yesterday, could not the "interview" and the "question" be similarly reoriented? Should not the one interviewed be the non-applicant rather than the applicant and the question — "Why not Medicine?" rather than "Why Medicine?"

Why not, indeed? The negative question makes sense, and the intelligent young student should have little trouble stating his objections to a medical career. The perceptive interviewer should have even less difficulty analyzing the answers, and examining them in the light of his own knowledge of the nature of his vocation. He can then decide whether the objections put forth by the interviewee are valid or not, whether they are based on a true conception of Medicine or on a complete misconception. If they are founded on a realistic appraisal of the difficulties inherent in the study and practice of Medicine — the long hours of study, the many years of preparation, and the few decades of arduous work — then they are, indeed, irrefutable. If, however, they are rooted in some misconception, then the interviewer should take great pains in refuting the objections with the view of inducing a reassessment of the potential candidate's intentions, and his possible recruitment into Medicine.

Let us take a cursory look at some of the current misconceptions and sharpen our refutations. A common misconception is the deluded view that Medicine is a monolithic profession demanding a well defined personality type with distinct interests, aptitudes, temperament and outlook on life. "What," asks the starry eyed young man, "would I be doing with the little black bag, I, whose destiny it may be to probe the mysteries of interplanetary space?" There should be little difficulty in convincing the youngster with the penchant for grandiose research that Medicine too has great mysteries to be fathomed by a probing mind. "What," asks the shy, thoughtful, introverted young student, "can this competitive, high pressured, rat-racy craft offer to me, whose taste runs to plain living and high thinking?" It should be easy to acquaint this objector with the opportunities that await him in the halls of academic Medicine and various medical institutions. It may be a little more difficult to sway his opposite number, the aggressive, extroverted, rugged individualist who resents regimentation and fears the advent of State Medicine. It should not be impossible, however, to allay these misgivings by pointing out that neither is socialized medicine an inevitability, nor is it likely that in a free society there ever will be a complete suppression of the competitive spirit

There will be doubters from the ranks of the mechanically minded, the administration oriented, the literary gifted, the philosophically inclined. They can all rest assured of finding outlets for their talents in the rapidly expanding areas of medical biomechanics, medical engineering, medical administration, medical thinking and writing. Those with a flair for travel will find opportunities in various global international medical projects, while others fond of hearth and home need not move out of their home town.

An earnest argument may come from the ranks of introspective young people, given to self-analysis, who on finding that they are not motivated by a strong desire to help suffering humanity, feel that they are not meant to be doctors. Before we get tempted to agree with them let us hear what Dr.

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Sjent-Giorgyi has to say on the subject. "People who have the desire to be useful to mankind and go into research to alleviate human suffering," states the famous biochemist, "should work in the field of charity, not that of research. Research requires egotistical people who seek their own pleasure and satisfaction in solving the puzzles of nature." Not only in the field of research but in the practice of Medicine excessive sympathy and self identification with the patient may be more detrimental than beneficial to good medical care. It is not sympathy, but empathy—the art of projecting oneself into the contemplated problem and understanding the patient, that is the most valued quality a doctor can possess, and this quality can be cultivated. Thus, our conscientious objector can be shown that he too, is a welcome recruit.

It can be readily seen that many objections to a medical career are really minor reluctances that can be overcome. They stem from lack of appreciation of the multifaceted character of Medicine and her vast scope. The average student unacquainted with the multicolored map of Medical territory fails to discern areas of inviting familiarity.

It is up to the old travellers to steer them right.

Ed.

Book Reviews

A Synopsis of Contemporary Psychiatry. Ulett and Goodrich. Second Edition. The C. V. Mosby Co. $6.50.

This is a pocket sized book of two hundred and ninety-seven pages. There isn't much redundancy or word wastage. The result is that it contains a great amount of information in a small compass. The emphasis is, by design, on practical matters; theory is deliberately omitted. The information is accurate and does, for the most part, reflect the current North American point of view—at least one of the most commonly accepted which recognizes that both early experiences and organic factors have relevance in the etiology of mental illness. From this follows, that in treatment, physical means and psychotherapy are helpful, and this premise is accepted in the book.

The fact that the book has gone into a second edition attests to its usefulness. No doubt, no one book could fill the needs of all those mentioned in the preface of the first edition. The authors mention: nurses, medical students, general practitioners, beginning residents in psychiatry and others. However, it does serve very well as a quick reference for those matters which it does cover, and its greatest usefulness is probably for the medical student who would have lectures to amplify and explain the material.

The book is divided into three sections. The first covers the examination of the patient and includes a brief description of many of the most popular of the psychological tests used today. The senior author is particularly interested in the Rorschach and has designed a short cut method of interpretation by which some useful information can be obtained. This method is briefly described.

The second part is devoted to describing the clinical syndromes and the salient points are covered, but leaves one with a feeling of too great brevity.

The final section deals with therapy and forensic psychiatry. There are sixteen pages devoted to psychotherapy and fifty-five pages devoted to physical therapies. Necessary space is given to the newer drugs as well as the older physical therapies. In view of the limited space, there seems to be a greater than necessary striving to include as many types of the physical therapy as possible, even the seldom used ones.

J. Matas.

The Essentials of Perimetry. Howard Reed, M.B., M.S. (Lond.), F.R.C.S. (Eng.), F.R.C.S. (Can.), F.A.C.S. Cloth, 192 pp., with 167 illustrations. Toronto, Oxford University Press, 1960. $6.25.

The purpose of this monograph is to provide a simple account of the basic principles of defects in the field of vision. The book serves as an introduction to the subject for students and provides an excellent revision for the practitioner.

The subject matter is presented in large easy to read type which is enhanced by the excellent line drawings of Miss Nancy Joy. The author's style is clear and succinct and provides enjoyable reading. The account has been kept brief and without redundancy and this is reflected in the modest price of the volume.

The subject matter has been divided into three sections: the anatomical; the normal field and methods of examination; and field defects with interpretation.

This reviewer found only one discrepancy which should be noted by the author: the text and figure 117 are not in agreement.

An excellent list of other textbooks and references pertaining to the subject are included.

This text is recommended as an excellent introduction to the subject for the student and also as a valuable revision for the practitioner.

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Heredity in Ophthalmology, by Jules Francois. Published The C. V. Mosby Co., St. Louis. Price $23.00.

My former chief, Professor Arnold Sorsby of London, England, who wrote the first book in English on genetic aspects of ophthalmology, often said that the study of genetics is increasing so much in scope and importance that ophthalmology is tending to become but a branch of genetics. Of course, no ophthalmologist would agree with this suggestion, but the range of Professor Francois' book on genetic aspects of ophthalmology makes one realize that the statement does contain some truth.

Francois' book, "Heredity in Ophthalmology" first appeared in French in 1958 and it has now been translated by the author himself into excellent English. It is divided into four parts. The first part contains a lucid description of the elements of genetics. The various types of inheritance are readily understood. There is even a chapter on the rudiments of statistics and biometry.

Part two examines the varieties of inherited diseases and discusses the detection of carriers of such diseases. Treatment and prevention are outlined in order to indicate how much can now be done for many of the hereditary diseases which were once incurable.

The third part of the book is an encyclopedic review of the hereditary aspects of ocular diseases. Refractive errors, glaucoma, strabismus, cataracts, retinoblastoma, retinitis pigmentosa, detachment of the retina and many other conditions appear in this section. In fact it seeems that apart from the inflammatory group there are few ocular diseases which may not be inherited.

In the last part consideration is given to inheritable general diseases which have ocular manifestations. These include a fascinating collection of metabolic disturbances, affections of the central nervous system, and skeletal, skin and blood diseases. The very last chapter of the book is a valuable collection of the various hereditary syndromes.

This book can be recommended without reservation to all ophthalmologists and all physicians who have an interest in genetics. It is a mine of authoritative information.

Howard Reed.

☆

Medical Pharmacology. Principles and Concepts. Andres Goth, M.D., Professor of Pharmacology and Chairman of the Department of the University of Texas, Southwestern Medical School, Dallas, Texas. The C. V. Mosby Company, St. Louis, 1961. 551 pp. Price $11.00.

In no other medical discipline is the difficulty of seeing the wood for the trees more apparent than in Pharmacology. The trees are much too numerous to permit a panoramic view. Hence, the classical voluminous standard text on this subject is of value only as a reference book for those interested in details of some particular drug action. Its index of readability is otherwise very low.

To this unhappy rule Goth's Medical Pharmacology presents a most welcome exception, for it is an ideal answer to the student and physician in quest of a lucid presentation of essential information about drugs with emphasis on principles and mechanisms underlying their mode of action rather than petty irrelevant details which obscure fundamentals and overcrowd memory. This emphasis on the basic is apparent not only in the introductory chapter which deals with general aspects of drug action—receptor concept, enzyme inhibition, membrane phenomena, interaction with endogenous regulators of cellular functions, toxicity, side effects, hypersusceptibility, idiosyncrasies, allergy, cumulation, tolerance, tachyphylaxis, etc. — but throughout the book where every chapter is preceded by a brief outline of the mode of action of drugs under discussion, and every drug discussed in the light of above current concepts.

The book is compact. Yet no significant drug likely to come within the orbit of the physician's interest is omitted. Even congeners are mentioned (mercifully with exemplary brevity). The current interest in psychopharmacology is reflected in prominence given to the subject in the three chapters devoted to it.

Although concise, the book is not synoptic. It has style and elegance and is eminently readable. In fact, it competed successfully with a few whodunits in this reviewer's repertory of vacation-time reading.

S. V.

☆

Symposium on Anticoagulant Therapy. Edited by Sir G. W. Pickering. Harvey & Blythe Ltd., 1961. 21s.

This publication is a report of the proceedings of a symposium held at the Royal Society of Medicine on 18th and 19th November, 1960. Most of the participants were from the British Isles, with Owren (Norway), Koller (Switzerland), Nicola (Italy) from continental Europe.

The first sessions dealt with mechanisms of action of the oral anticoagulants and the laboratory control of this therapy, including a discussion on the thrombotest. Many points were raised in these discussions, and it was pointed out that while much attention is paid to the "safe" levels, in order to avoid bleeding as a complication of such therapy, rather less attention is directed to what levels are really therapeutically effective. While the prothrombin estimation is an over-all measurement of a number of coagulation factors, empirically it has been of great use, with recognition of its limitations acknowledged, provided that the laboratory undertaking the assays is technically competent. Thrombotest has its advocates and its Doubting Thomases.

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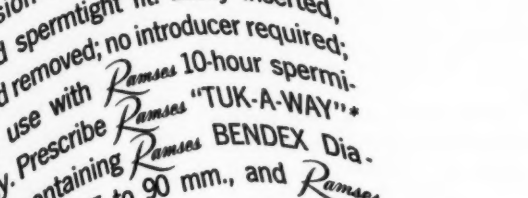

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The remaining discussions were more clinical, dealing with indications for anticoagulation therapy in short and long term aspects. It is rather distressing to discover so many recent papers differing so radically from the more classical ones on the value of short term anticoagulation therapy in acute myocardial infarction. Perhaps the differences can be attributed to a general change in the management of this disaster, with earlier ambulation. One has the feeling that the position on anticoagulation in myocardial infarction is now reversed, and it is the conservative point of view to use such therapy, and the angry young men who would discard it. Most of the participants in the symposium appeared to be men of practical experience, dealing with the clinical problems as a daily routine, and most upheld the value of such therapy.

There are many points raised in the discussions that are of practical interest, and this inexpensive book is recommended to anyone who is making use of anticoagulant therapy.

P. T. Green.

Victorian Order of Nurses

Several changes have taken place within the Winnipeg Branch of the Victorian Order of Nurses during the past months.

The marked increase in requests for Home Nursing to residents of Metropolitan Winnipeg necessitated the appointment of two additional nurses in January, bringing the total staff to twenty-eight. Monthly visits averaged 3,960 as compared with 3,410 last year. This increase in requests for services would indicate that Victorian Order service is recognized as an alternative to institutional care. Studies have shown that hospital beds can be released for more acutely ill patients and the service is less costly than in an acute treatment hospital. There are many conditions that must be treated in hospital for at least part of the illness but it is now recognized that care in the familiar normal surroundings of the home, as soon as possible, brings about a greater desire for recovery and a more complete return to independence.

The Board of Management had for some time been aware of the necessity for additional office space and early this year a second office was opened at 865½ Main Street. A supervisor, twelve staff nurses and one clerical worker, moved from the main office in the Medical Arts Building, now provide Victorian Order service to the citizens of Metropolitan Winnipeg who live in Transcona, the Kildonans, East and West St. Paul, Brooklands, Weston and Rosser, as well as that area of Winnipeg north of Ellice Avenue between St. James and the Red River.

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Sodium phenobarbital	45 mg. (¾ gr.)
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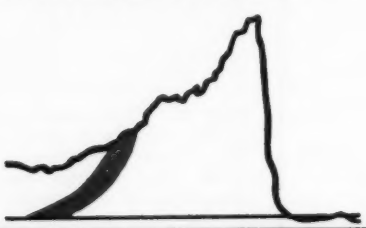
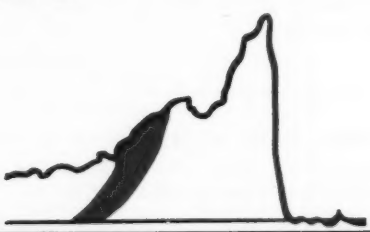
Before Peritrate—Tracing shows reduced coronary blood flow (shaded area) after myocardial infarction.[3]

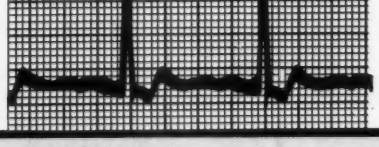


After Peritrate—Significant increase in coronary blood flow of postcoronary patient.

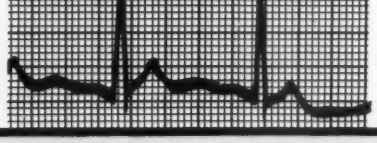


ECG response to standard exercise shows: A 20 mg. dose of Peritrate "... affords protection for four to five hours . . ."

Before Peritrate—Exercise ECG shows ST segment depression.



After Peritrate—Exercise ECG shows normal ST segment.



Peritrate is safe—causes no change in cardiac output,[2] no significant change in blood pressure or pulse rate.

1. Johnson, P. C., and Sevelius, G.: J.A.M.A. 173:1231 (July) 1960. 2. Sevelius, G., and Johnson, P. C.: Use of Radioisotopes to Record Myocardial Blood Flow Changes Produced by Coronary Dilators, Scientific Exhibit, A.M.A. Meeting, Miami, Fla., June, 1960. 3. Russek, H. I.: Postgrad. Med. 19:562 (June) 1956.

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It was a long time ago when I first had the "dream." It was not a pleasant dream, nor was it a nightmare. Nor for that matter was it particularly unusual — thousands must have dreamed about missing a train or some other moving conveyance. In my dream it was not a train but a horse-drawn sleigh, the usual winter transport in the rural community where I practiced medicine, that I saw depart just as I was about to alight.

I should have forgotten the dream, had it not been for its regular recurrences during the ensuing year. Realizing that the dream had psychiatric implications, I began to delve into psychoanalytic literature. Here a perfectly logical and simple explanation awaited me. Moving vehicles — it would appear — symbolize passing opportunities, once missed never to be recaptured. Having found a plausible explanation, I proceeded to excavate my subconscious for unfulfilled ambitions in an effort to unearth the culprit of the dream. The digging was not at all difficult, for it soon became obvious that what I craved most at the time was city life with its bright lights and rich culture—museums, art galleries, burlesque shows, operas, night clubs, horse races, and supermarkets.

Having laid my finger on the source of my maladjustment, I quickly transplanted myself from the good earth of the country to the asphalt jungle of the metropolis. This deracination was painful, but I thought it was a small price to pay for the eradication of the dream. Unfortunately, the dream persisted, unchanged but for the vehicle, which was no longer an unsophisticated sleigh but a solid gold Cadillac, chauffeur and all. The variation on the theme, however, did not change its basic unpleasantness. Running after a speeding primadonna of the highway proved no less frustrating than chasing the backside of a horse. Why did the dream persist? What was passing me by? Could it, perchance, be money—the lure of gold symbolized by the glittering automobile?

Proceeding on this assumption I began a systematic pursuit of wealth. My effort was well rewarded. My stocks skyrocketed, my practice flourished, my investments paid handsome dividends—I prospered. The dream, alas, remained. No longer a car, but a boat—a big beautiful ocean liner was sailing away just as I was approaching the gangplank. This time I was stymied. I was no longer sure of anything. An "educated" guess, however, led me to assume that at the bottom of my frustration was a desire for honors and degrees, which could only be acquired in distant lands and far away places.

Being a man of action, I followed my "hunch" with a systematic thoroughness. Combining travel with study, I succeeded in acquiring all the attainable honors and degrees that Academic Medicine can bestow upon an ambitious aspirant. Did the dream vanish? Not at all. It was there to torment me with yet another heartbreaking sight—that of an elevator closing its doors in my face and ascending without me. Was this perhaps a reminder of the higher things in life that eluded me? While pursuing material pleasures, did I neglect the higher values? Acting on this possibility, I devoted every spare moment of my time to the study of philosophy, theology, literature, and art. But did the dream forsake me? Unfortunately not.

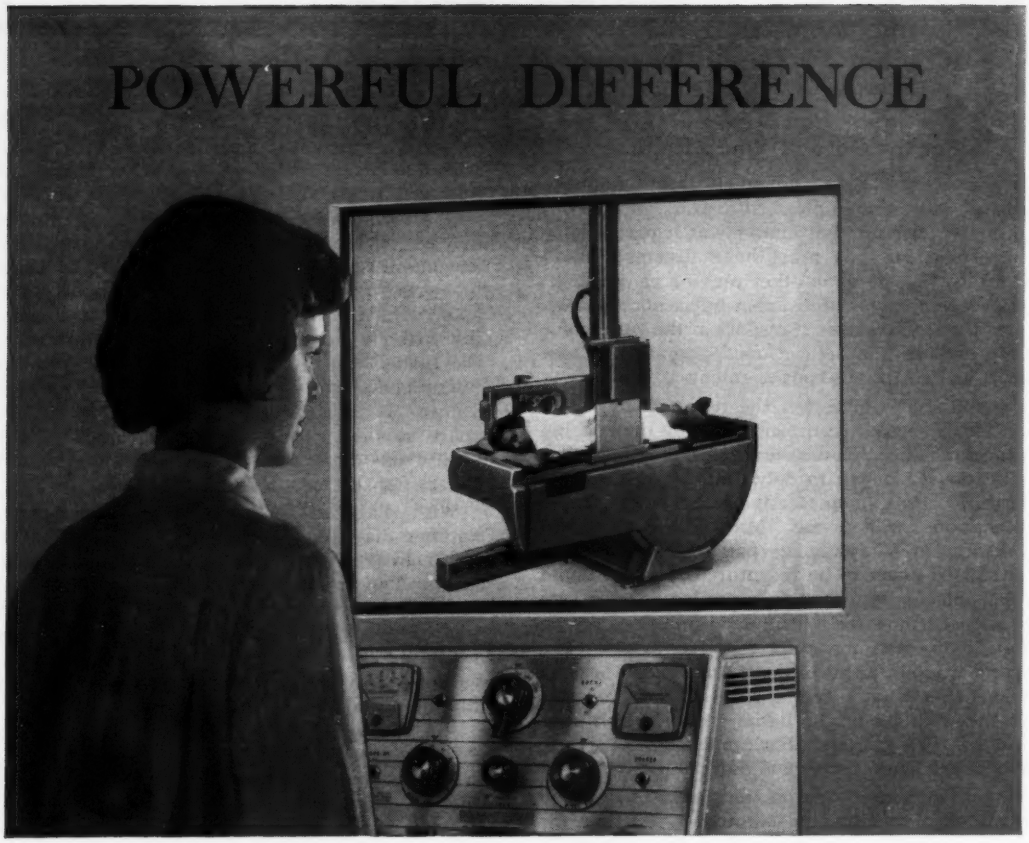
With diabolical cunning it reappeared in yet another disguise. Now it was a bus loaded with small children supervised by a stern-looking schoolmarm. The implication was obvious. I was missing marriage and its blessings. Quickly and unhesitatingly I proposed to the first eligible maiden who would have me, married her, and proceeded to raise a family. Luck was with me again. My family did me proud.

But how about the dream? Yes, it was there—not a car or a boat, but a beautiful gondola gliding smoothly along the Grand Canal paying no heed to my supplication to be taken aboard. Desperate for a solution I went to a psychoanalyst. Lying down beside me on the couch—the interview took place in Paris—she calmly suggested that my frustration was obviously the "natural" need of a mistress. This, she intimated, was the "normal" ambition for a man of my status in society—the "correct" thing to aspire to. It was only too clear that my analyst took no cognizance of the moral temper prevailing in my native land. I forgave her, obviously rejecting her explanation.

What was I to do? In quiet desperation I went to my old family physician, a man of kind understanding and earthly wisdom. Absently listening to my story, he handed me a bottle of green pills. "This," he said, "is Profanil, the latest thing for mental ills. Last year I used Martinid, and the year before Preburpin; they are now obsolete. Profanil is the up and coming thing. It can't miss."

I took the pills mechanically, no longer listening to his chatter. Something clicked. Thoughts began to spin feverishly in my brain. Martinid, Preburpin, Dexedrix, Sardil — all gone and forgotten, along with a host of other drugs prescribed by doctors on countless occasions. But have I used them? Hardly ever. Being slow in my responsive enthusiasm, I never got around to prescribing a drug before its obsolescence. It was obvious that the things that eluded me were drugs that rode crests of waves, while I was helplessly inert.

Reprinted from the Journal of the American Medical Association, March 25, 1961.



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Having stumbled upon the great discovery, I quickly rose to the occasion. Buttonholing all visiting drug house representatives and avidly seizing their promotional literature, I proceeded with great dispatch to prescribe the new and wondrous medicaments to all and sundry. I became a prolific prescriber — the friend of the pharmacist and the delight of the "detail" man. I allowed no new drug to elude me. Indeed, I went all out with high hopes for the ultimate elimination of the dream.

My hopes did not come true, but neither were they completely unfulfilled. The dream persisted, but it was a fundamentally altered vision. The moving vehicle was there, and so was I, still running, but—mirabile dictu—no longer left behind. A few brisk steps, and here I was entering the conveyance, whatever it happened to be, taking my rightful place among my fellow passengers, I had finally arrived.

My happiness, however, was short lived. As the novelty of boarding and alighting wore off, I began to take cognizance of some rather unpleasant phenomena. My fellow passengers, erstwhile a bright and cheery lot, acquired a fixed expression of monotonous fatuity. The countryside through which I was passing, vaguely familiar at first, soon began to acquire the features of a landscape déjà vue. Worst of all, my destination—the eagerly anticipated terra nova—turned out to be so much like the point of departure, that I had the feeling I had never left the latter at all. Was I travelling in circles?

My nights continued to be plagued by dreams; my days, dedicated to prescribing, I became morose, irascible, and very short with my patients. Only today, as I was tossing off the very latest variant of a masterful combination of an antibiotic, antitussive, antidepressant, antispasmodic antacid in a slow-release capsule, and was about to prescribe an additional tablet containing a multivitamin, hematinic, steroid, aphrodisiac tranquilizer, I heard my patient remark timidly that he hoped the pill would be less costly and more effective than its two score and ten predecessors. The remark, for some reason, incensed me. At a loss for a prompt and apt answer, I blurted out, "Do you think I am here for the good of your health?"

Perhaps it is time for me to see my psychiatrist again—the one in Paris, of course.

M. Y. Alterego.

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Association Page

1961 Legislation of Interest to the Medical Profession

Bill 3 — An Act to facilitate Cornea Transplants from the Bodies of Deceased Persons to Living Persons.

Bill 15 — An Act respecting The Department of Welfare.

Bill 16 — An Act respecting the Department of Health. By this Act and another Act to be introduced at this session the Department of Health and Public Welfare is being divided and made into two separate departments. The present bill will deal with the new Department of Health.

Bill 19 — An Act to repeal The Health and Public Welfare Act and to amend Certain Other Acts. These amendments are consequent upon the division of The Department of Health and Public Welfare into two departments; namely: The Department of Health and The Department of Welfare.

Bill 40—An Act to amend The Hospitals Act. 1. Hospital, medical staff by-laws. 2. Tissues.

Bill 59 — An Act to amend The Liquor Control Act. The provision repealed puts upon physicians the onus of proving that liquor prescribed for a patient was bona fide and for medical purposes.

Bill 64 — An Act for granting to Her Majesty Certain Further Sums of Money for the Public Service of the Province for the Fiscal Year ending the 31st day of March, 1961.

VIII — Health and Public Welfare

3. Welfare Division		
(a) Public Welfare Services:		
(3) Social Allowances	$120,000.00	
(6) Assistance for Municipal Aid Expenditures	530,000.00	$650,000.00

Bill 78 — An Act to amend The Pharmaceutical Act. 1. The definition is changed to conform to FOOD AND DRUGS ACT (Canada). 2. The definition of "Medical practitioner" is changed to conform to The Interpretation Act. 4. The definition is expanded to include a dispensary in a public hospital. 9. This amendment permits the discipline committee to exercise disciplinary powers. 10. This amendment provides for the appointment of a discipline committee. 12. This amendment allows the code of ethics of the association to deal with licensed pharmacies. 20. This amendment excludes sales of medicine by vending machines and to bring the prohibition into line with Federal Acts.

Bill 79—An Act respecting The Winnipeg General Hospital.

Bill 80—An Act to amend The Child Welfare Act.

Bill 85—An Act to amend The Health Services Act. 1. This amendment provides that The Regulations Act does not apply to regulations made under The Health Services Act establishing, dissolving, or altering local administrative committees.

Bill 95—An Act to amend The Workmen's Compensation Act. (2)

2. Previously, where an injury was attributable solely to wilful misconduct, no compensation was payable unless the disability resulting therefrom was both serious AND permanent. This is changed so that compensation may be granted where the disability is either serious OR permanent.

Bill 99—An Act to amend The Motive Fuel Users Tax Act. 1. and 3. Raises the general tax from eleven cents to seventeen cents per gallon. 2.(a) Raises from one to two cents the tax on certain users of motive fuel. 2(b) Removes the one cent tax on motive fuel used for propelling aircraft since such fuel is now to be taxed under The Gasoline Tax Act.

Bill 100—An Act to amend The Hospital Debentures Guarantee Act, 1960. This increases from $450,000.00 to $700,000.00 the amount of the moneys payable under debentures of The Dauphin General Hospital that can be guaranteed by the government.

Royal Commission on Health Services in Canada

The Chairman of the Committee producing a brief to the Royal Commission wishes to stress the importance of members submitting material for the Committee's consideration.

Many members of the Association are now preparing subject material for Brief and review and collation of these items is now taking place. It is expected that a considerable number of meetings will take place prior to the final production.

The Commission is holding a preliminary hearing in Ottawa on September 27th. The C.M.A. will be represented and submit a report to the Commission.

Provincial briefs will be heard commencing with the eastern provinces in October. It is anticipated the Commission will sit in Winnipeg during January 15th to 19th.

R.P.H.S.

Narcotic Control Act and Regulations

Attention of all medical practitioners is directed to the Narcotic Control Act and Regulations, also to the amended Food and Drugs Act and Regulations which have been proclaimed effective September 15th.

Circular letters No. N513 and N514 will be sent to medical practitioners on or about September 15th.

If you have not received a copy, kindly communicate with the Department directly or with this office.

M. T. M.

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V4540-1

Questions and Answers Page

In order to keep the medical profession informed as fully as possible in all matters relating to Association business, medical economics and prepaid medical care, this page welcomes questions pertaining to these fields.

Question: Is medical care of patients in extended treatment centres or chronic care hospitals a shareable cost under the Manitoba Hospital Services Plan?

Answer: No.

When this matter was studied the Association agreed to a temporary arrangement wherein this would occur until such time as a joint C.M.A.-C.H.A. Committee set up to study the matter, reported.

However, at this time the Federal Government will not allow clinical medical services to be a shareable cost under the Hospital Plan and this is also the attitude that the C.M.A. supports.

This does not affect physicians acting in an administrative capacity, as their incomes are now considered a shareable cost.

The matter of payment for full-time and part-time clinicians in chronic care hospitals is now being jointly studied by the Association and the Minister of Health.

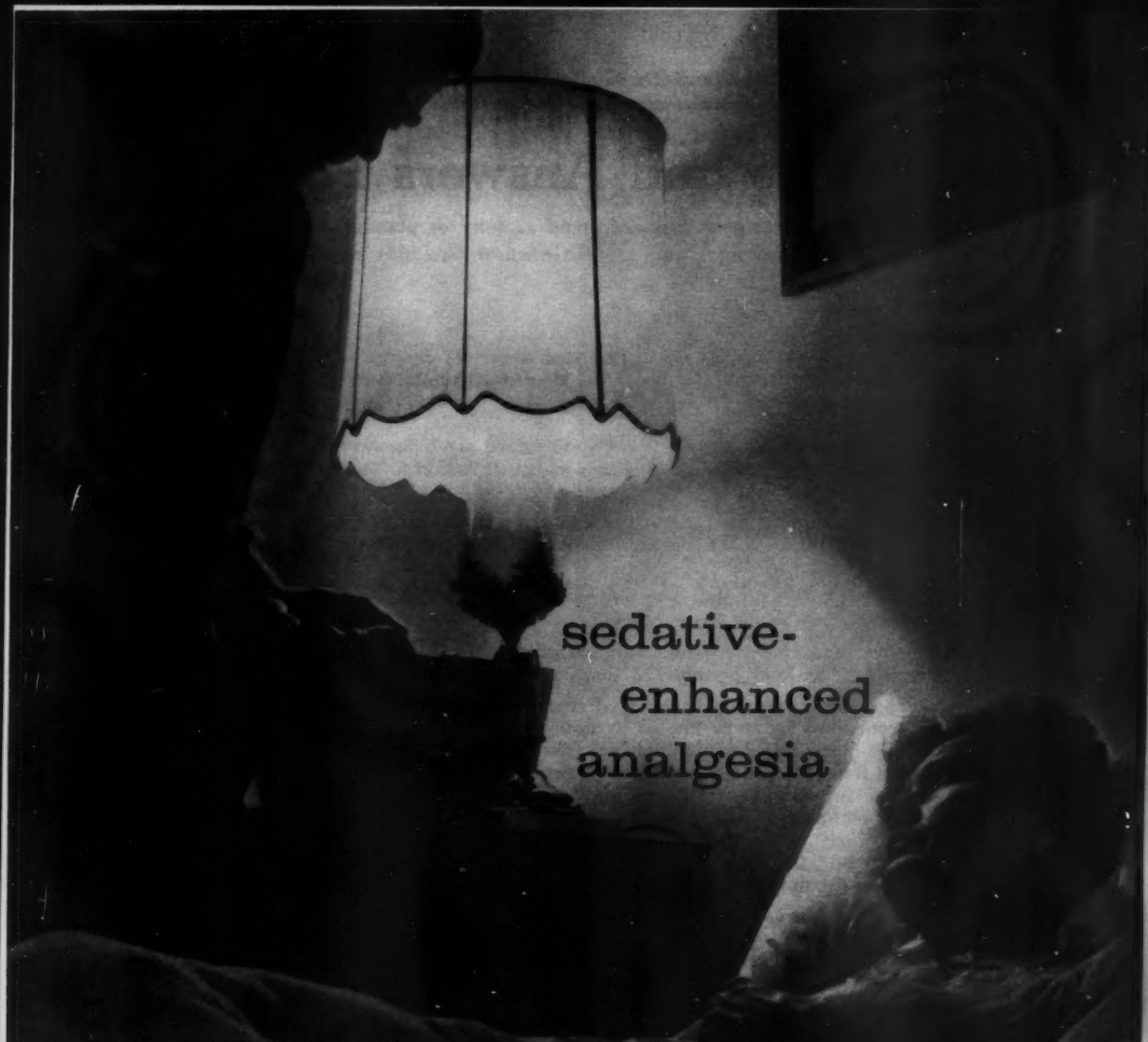
There appears to have been agreement reached in the principles involved and the doctors concerned are to be invited to discuss the matter with the Association's representatives before any commitments are officially made. The doctors concerned are, of course, free to negotiate on their own behalf although it would appear more desirable to make these arrangements through the Association and full co-operation and assistance will be available on behalf of the Association.

Question: What steps are being taken by M.M.A. to prepare a presentation to the Royal Commission on Health Services?

Answer: Herewith a reply from Dr. K. Rankine Trueman, chairman of the committee preparing the brief:

The Royal Commission on Health Services

The Manitoba Medical Association will submit a brief to the Royal Commission when it holds hearings in Winnipeg in January. The purpose of the Commission is to determine the nature and scope of facilities available in Canada for the provision of health services to all parts of the population. It is expected that the Commission will be able to assess our resources, determine what is needed and recommended in what areas and by what means increased benefits may be introduced into the health field. Such a study is a most natural one. It should permit an enlightened conclusion to be reached by all forms of government and all varieties of political parties in achieving a solution of a problem not universally understood. The Manitoba Medical Association is pleased to co-operate with the Commission and will strive to present all factual information it can gather applicable to its terms of reference. Much work of a research nature is being done by members of the association which will be processed in the near future. The profession in general, local medical societies and specialty sections have been invited to contribute to the work of the committee compiling the brief. THERE IS STILL TIME TO PRESENT COMMENTS AND ADVICE.



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1. Meyers, G. B.: Ind. Med. & Surg. 26:3, 1957. 2. Murray, R. J.: N. Y. St. J. Med. 53:1867, 1953.

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Social News

Reported by K. Borthwick-Leslie, M.D.

Gleaned from "Through the Years" Alumni Journal

1924—Dr. Donald Black, Kamloops, B.C. is now director of the North Shore Health Unit, covering both North and West Vancouver.

☆

1927—Dr. Alan A. Klass, past president of the U. of M. Alumni Association, has been elected Honorary President of the Student Union.

☆

1938—Dr. W. Donald Ross has been appointed Professor of Psychiatry, University of Cincinnati, Ohio.

☆

1939—Dr. A. B. Houston has been appointed associate medical director of the Great West Life Assurance Company, Winnipeg.

☆

1947—Dr. Frederick Waugh, B.Sc. 1947, M.D. 1953 is associated with the Dept. of Medicine, Winnipeg Clinic.

☆

1950—Dr. Gerhard Friesen received his Master of Science in Surgery June, 1961 from the University of Minnesota.

☆

1951 — Dr. Bernard Kredenster is now doing Obstetrics and Gynaecology in Edmonton, Alta.

☆

1952—Dr. Theodore Harris is resident in Psychiatry, Nebraska Psychiatric Institute.

Dr. Colin Sinclair, B.A. 1952, M.D. 1957, B.Sc. Med. 1957 attended convocation exercises, U. of M. when he received his M.Sc. Med. 1961. He is at present doing post graduate work in Salt Lake City.

☆

1954 — Dr. Daniel Shapira is now Assistant Professor of Surgery, New Rochelle, New York.

Dr. Leonard Levine, formerly Cleveland, Ohio, is now Urologist Associate of the Grand Forks Clinic, Grand Forks, N.D.

☆

1955—Dr. John C. Sinclair, 1959, is doing post graduate work in paediatrics at the Columbia Presbyterian Medical Centre, New York.

☆

1957—Dr. Walter J. Heichman is completing his P.G. training in surgery, Saskatoon City Hospital, having done a year in Pathology.

☆

1957—Dr. Paul Portnuff is doing Pathology at the Cook County Hospital, Chicago.

☆

1959—Dr. Kenneth Walton is doing post graduate work in Urology in Johns Hopkins Hospital, Baltimore.

Dr. J. W. Enns, formerly of Vancouver, in July 1961 started in General Practice in Grandview, Man. That I didn't know, Dr. Enns!!

☆

From 1959 to 1961 — no news except our local ones:

Karl Riese, M.D., F.R.C.S. (C) announces the opening of his office, 325 Medical Arts, Winnipeg, specializing in Tumor Surgery.

Jaroslaw Barwinsky, M.D., formerly of Cleveland, Ohio, announces the opening of his office, 218 Medical Arts, Winnipeg—Thoracic, Cardiovascular and General Surgery.

☆

Dr. and Mrs. Murray William Hollenberg left recently for New York, where Dr. Hollenberg will do post graduate work in Ophthalmology in the Manhattan Eye, Ear and Throat Hospital.

☆

Dr. John C. Peters, Winnipeg General Hospital, has been awarded the Wyeth Laboratory residency fellowship in paediatrics at the Children's Hospital, Winnipeg.

☆

Dr. and Mrs. Colin C. Ferguson are enroute to Stockholm, where Dr. Ferguson will address the annual meeting of the British Paediatric Surgical Association.

☆

Mrs. E. L. Lansdown (Dr.) of Toronto with children, is visiting her parents Dr. and Mrs. W. M. Musgrove. Mrs. Lansdown, matron of honor for the Schneider - Lansdown wedding, will also visit with Ted's parents, Dr. and Mrs. L. P. Lansdown.

☆

Lt. Richard Hitesman, R.C.N. and Mrs. Hitesman of Victoria, B.C. have been visiting his parents, Dr. and Mrs. R. J. Hitesman.

☆

Dr. and Mrs. Robert Gibson, Portage la Prairie, announce the engagement of Jennifer Yuill to Dr. Noel Winston Haukabo of Swift, Minnesota. The wedding will be Sept. 30, 1961 at St. Andrew's River Heights United Church.

☆

University Chapel, St. Andrew's, Scotland, July 28, 1961 was the site of the wedding of Frances Murray Macfarland, daughter of Dr. and Mrs. Maxwell Macfarland to Dr. Alastair Harris Imrie, son of Dr. and Mrs. S. Imrie, Edinburgh.

The bride is a graduate in Arts of United College, Winnipeg and the groom in Medicine from St. Andrew's University, Scotland.

The young couple will reside in Hanover, New Hampshire, U.S.A. where Dr. Imrie is engaged in medical research.

☆

Dr. and Mrs. J. C. McCawley announce the birth of their son, Aug. 28, 1961.

☆

Dr. and Mrs. Gary Beazley announce the arrival of Gordon Tyson, Aug. 26, 1961.

☆

Dr. and Mrs. B. M. Carleton announce the arrival of their second son, Craig, August 25, 1961.

☆

Happy holiday to me—Dr. K. Borthwick-Leslie.

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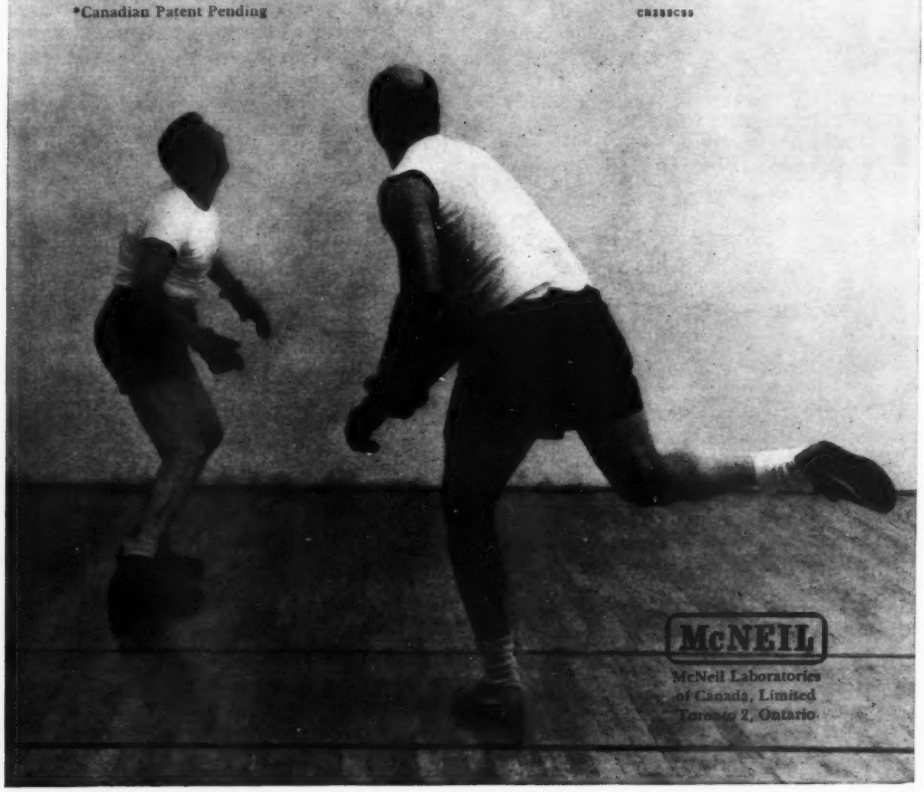

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HOSPITAL MEETINGS

Hospital	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Children's	12:00 Surgical Rounds	10:00 Staff Rounds "B" Service 12:00 Postgraduate Seminars	9:30 Staff Rounds "C" Service 11:00 Clinical Path. Conference	11:00 Grand Ward Rounds	10:00 Staff Rounds "A" Service	9:00 Newborn Conference
Deer Lodge	12:15 Clinical Luncheon (1st Monday)	8:30 Chest Ward Rounds 12:00 Surgical Ward Rounds	9:00 Gastro-intestinal Ward Rounds 1:30 Gross Pathology Demonstration 8:00 General Staff Meeting (Last Wednesday)	11:00 Medical Ward Rounds		
Grace	12:00-2:00 p.m. Weekly Seminar	Clinical Luncheon (3rd Tuesday)		12:00-2:00 p.m. Weekly Seminar		
Misericordia		12:30 Clinical Luncheon (2nd Tuesday, every 2nd month)				
Municipal			7:30 p.m. Review of Deaths (2nd Wednesday)			8:30 Clinical Staff Conf. and Ward Rounds
St. Boniface	11:00 Paediatric Rounds	11:00 Surgical Rounds	11:00 Grand Rounds 11:00 Cardio-Pulmonary Conference (2nd Wednesday)	8:00 Orthopedic Rounds 11:00 Tumor Clinic 11:00 Obstetrical Rounds 12:00 Clinical Luncheon (2nd & 4th Thurs.)	11:00 Medical Rounds 11:00 Cardio-Pulmonary Conference (4th Friday)	
St. Boniface Sanatorium		12:30 Clinical Luncheon (2nd Tuesday)				
Victoria		Tissue Committee (1st Tuesday)			12:00 Clinical Path. Conference (1st Friday) Clinical Luncheon (2nd Last Friday) Active Medical Staff (Last Friday)	
Winnipeg General		11:00-12:00 Medical Ward Rounds 4:00-5:00 Haematology Rounds	9:00-10:00 Tumor Clinic 12:30-1:30 Chest Conference	12:15 Clin. Luncheon (1st & 3rd Thurs.)	11:00-12:00 Neurology Rounds 12:00-1:00 Vascular Rounds	10:00 Surgical Conf. 11:15-12:15 Medical Conference
Brandon General			Medical Staff Lunch (Wed. prior to 2nd Tues. each month)			10:00-Noon Clinical Doctors from S.W. Manitoba invited (Nov. to May)

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• relief of the muscle tension and spasm which add pain to pain

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WINDSOR, ONTARIO

Report from Poison Control Centre

July, 1961

A Case of Carbon Tetrachloride Poisoning

In July, we saw one case of carbon tetrachloride poisoning. The patient was a 49 year old woman. She had consulted her doctor because of malaise, vomiting, back pain and oliguria of one week's duration. She was slightly jaundiced, had multiple ecchymoses over her face and trunk, ankle oedema, puffiness about the eyes, and tenderness over the liver. Careful questioning revealed that on the afternoon of the onset of her symptoms an eight ounce bottle of carbon tetrachloride had been dropped on the kitchen floor. The patient had mopped up the spilt contents squeezing the rags into the sink and flushing the liquid down with hot water. She then went on to prepare supper in the kitchen but by the time it was ready, was already feeling too ill to eat it.

The patient was admitted to hospital and her condition rapidly deteriorated. She became confused. Oliguria progressed to anuria and on the tenth day after exposure to the poison, there was still no sign of returning kidney function. She was extremely ill and it was decided to subject her to dialysis using the artificial kidney. On the 14th day of her illness she had a diuresis and thereafter her condition improved until it returned to normal.

This case is a classic example of poisoning by carbon tetrachloride inhalation. The physical signs demonstrated very nicely the main sites at which carbon tetrachloride exhibits its toxicity, namely, the liver, kidneys, central nervous system and the blood vessels. If there has been concomitant ethyl alcohol ingestion, the toxic effects of carbon tetrachloride are enhanced.

Poisoning may result from inhalation, ingestion, or absorption through the skin. The adult fatal dose by ingestion is three to five ml. The maximum acceptable concentration in air is contained in a room 50′ x 50′ x 15′ when eight ounces is spilt therein.

There is no known antidote to carbon tetrachloride poisoning. Cases must be treated symptomatically. Stimulants may induce ventricular fibrillation and are contraindicated.

Carbon tetrachloride poisoning is more common in industry than in the home. About twenty-five deaths are reported annually in the U.S.A.

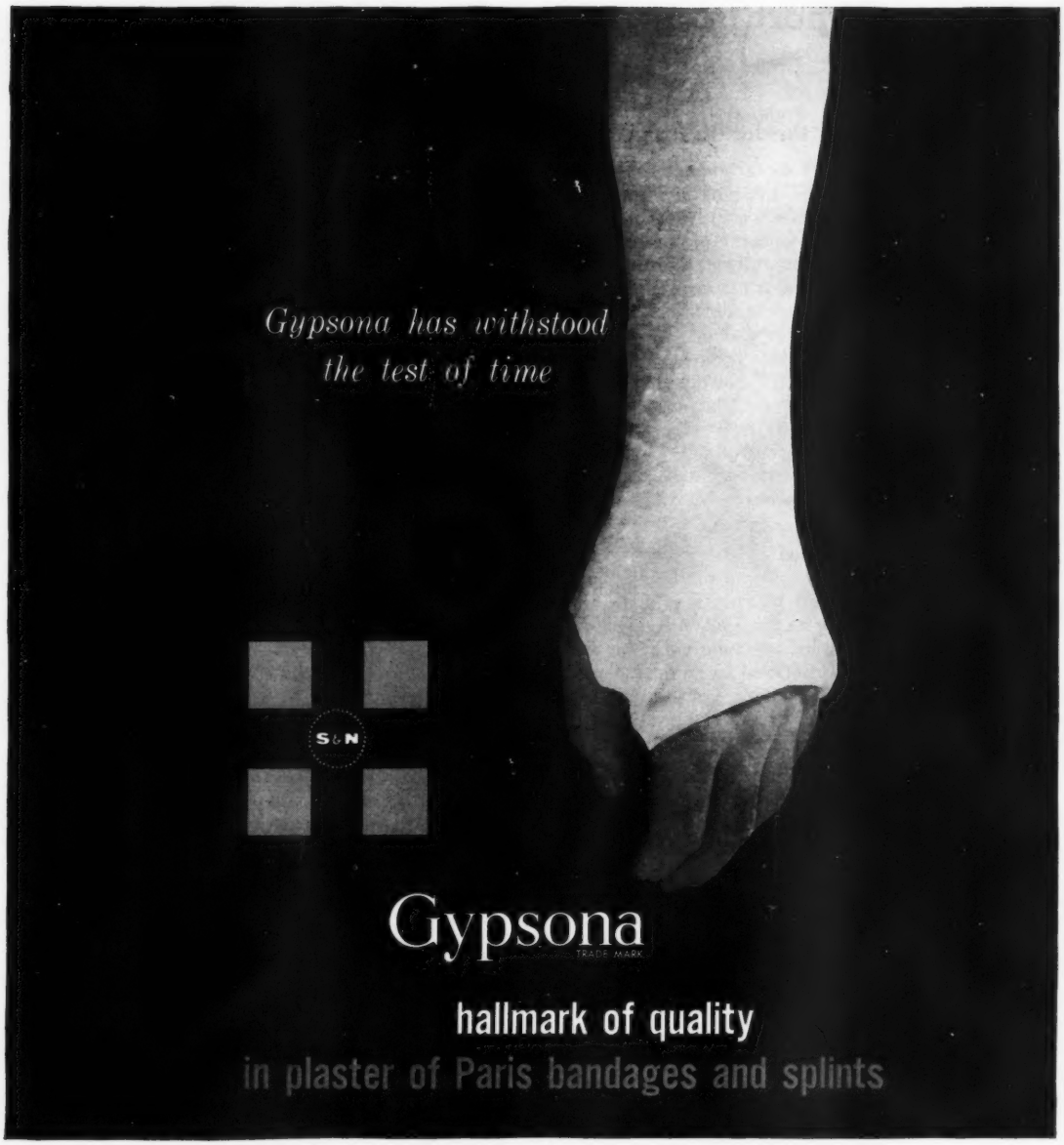
Vera Gellman, M.D., Director.

Poison Control Centre Report — July, 1961

	Toxic Content	No.	Disposal	
Drugs For Internal Use				
Aspirin	Salicylate	16	5/A	11/H
Coricidin	Caffeine, Aspirin, Phenacetin	1	1/H	
Asaphen	Salicylate and Phenacetin	1	1/H	
Phenobarbital	Barbiturate	1	1/H	
Butisol Sodium	Butabarbital Sodium	1	1/A	
Bendectin	Bentylol (Dicyclomine) Hydrochloride, Decapryn (Doxylamine) Succinate, Pyridoxine Hydrochloride	1	1/A	
Thyroid Tablets	Thyroid Extract	1	1/H	
Nitroglycerine Tablets	Glyceryl Trinitrite	1	1/H	
Dulcolax	(Bis)p-acetoxyphenyl (2-pyridylmethane)	1	1/H	
Paradione	3,5-Dimethyl-5-Ethyloxazolidine-2,4-Dione	1	1/H	
Miscellaneous Pills	?	5	1/A	4/H
Drugs For External Use				
Mercurochrome	Merbromin	1	1/A	
Camphorated Oil	Camphor	1	1/A	
Commercial Products				
Javex	Sodium Hypochlorite	1	1/H	
Turpentine	Hydrocarbon	4	4/H	
Kerosene	Hydrocarbon	1	1/A	
Johnson's Paste Wax	Hydrocarbon	1	1/H	
Liquid Wax	Hydrocarbon	1	1/H	
Lighter Fluid	Hydrocarbon	1	1/H	
Carbon Tetrachloride Inhalation	Halogenated Hydrocarbon	1	1/A	
Joy Liquid Detergent	Anionic synthetic detergent, Aqueous ethyl alcohol, fatty-acide amide	2	2/H	
Sani-Flush	Sodium Bisulfate	1	1/H	
Moth Ball	Naphthalene	1	1/H	
Rawleigh's Kreo	Coal Tar Derivatives	1	1/H	
Toilet Deodorant Block	? P-dichlorobenzene	1	1/H	
Silvikrin Shampoo	?	1	1/H	
Mouse Seed	Strychnine	1	1/H	
Rat Poison	?	1	1/H	
Nott's Dog-Check	Lemongrass Oil	1	1/H	
Antiperspirant Lotion	Polyol Monostearates, Polyol Monolaurate, Aluminum Chlorhydroxide complex	1	1/H	
Miscellaneous				
Perfume	Ethyl Alcohol	1	1/H	
Water Color	? Gum Cambogia	1	1/H	
Hydrogen Peroxide	Hydrogen Peroxide	1	1/H	
Rubbing Alcohol	Methyl Alcohol	1	1/H	

CODE: A — Admitted to Hospital.
H — Sent Home After Examination.

Total Patients Seen	57
Total Phone Calls	63
Total Patients Seen After Phone Calls	8
Total Admissions	11



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DEPARTMENT OF HEALTH & PUBLIC WELFARE

NOTIFIABLE DISEASE PICTURE

North of 53 District

Reports were received of one case of infectious hepatitis and one case of diphtheria. This was in a seven year old known treaty Indian at the Pas. He had been immunized with Diphtheria Toxoid in 1959.

Northwestern District

One case of scarlet fever was reported.

Northern District

No reports were received.

Brandon District

Reports were received of 5 cases of infectious hepatitis, one scarlet fever and one case of bacillary dysentery.

Central District

One case of scarlet fever was reported.

LIST OF DEATHS FROM NOTIFIABELE DISEASES
July, 1961

URBAN: Cancer, 80; Diarrhoea & Enteritis, 2; Jaundice (infectious), 1; Pneumonia Lobar (490), 1; Pneumonias (other forms), 17; Tuberculosis, 2; Late effects of acute infectious encephalitis, 1; Other deaths under 1 year, 18. Other deaths over 1 year, 260. Stillbirths, 11. Total, 393.

RURAL: Cancer, 24; Influenza, 2; Pneumonia Lobar (490) 1; Pneumonias (other forms), 7; Syphilis, 1; Tuberculosis, 3. Other deaths under 1 year, 10. Other deaths over 1 year, 154. Stillbirths, 8. Total, 210.

INDIANS: Pneumonias (other forms) 2. Other deaths under 1 year, 2. Other deaths over 1 year, 3. Stillbirths, 2. Total, 9.

Unorganized Miscellaneous

Reports were received of eleven cases of infectious hepatitis.

General

The incidence of reportable communicable disease has been particularly low. The most commonly reported disease remains infectious hepatitis of which forty-seven reports were received. This is lower than the incidence in recent months. Note should be made of the three cases of brucellosis. These occurred in employees at a meat packing plant and to date this year there have been ten cases of brucellosis from this source. In the province as a whole, reports have been received during 1961 of twenty-one cases of brucellosis.

Winnipeg District

Three cases of brucellosis were reported. There were also twenty-nine cases of infectious hepatitis, eight cases of bacillary dysentery, three diarrhoea of the newborn, two food poisoning and one scarlet fever.

Southern District

One case of infectious hepatitis and two cases of scarlet fever were reported.

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The meeting will be divided into three sections: Medicine and Paediatrics, Obstetrics and Gynaecology, and Surgery, and will be held at the Hotel Saskatchewan. The programme will include presentations by a number of highly qualified guest speakers.

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